UNIVERSITY OF MICHIGAN
DEC 26 1950
MEDICAL LIBRARY

BRITISH MEDICAL JOURNAL

JOURNAL OF THE BRITISH MEDICAL ASSOCIATION

SATURDAY DECEMBER 2 1950

TABLE OF CONTENTS

Protein Structure and Clinical Problems E. C. DODDS, M.V.O., M.D., F.R.C.P., F.R.S. 1237

Regulation of Secretion of Cortical Hormones MARTHE VOGT, M.D., Ph.D. 1242

Objective Assessment of Improvement in Rheumatoid Arthritis O. JANUS, M.B., B.SC., M.R.C.P. 1244

Alopecia Areata : A Clinical Study IAN ANDERSON, M.B., B.SC., M.R.C.P. 1250

Treatment of Thyrotoxicosis with 2-Mercaptoimidazole GEORGE L. FOSS, M.D. 1252

Intravenous Iron in Hypochromic Anaemia Associated with Rheumatoid Arthritis R. J. G. SINCLAIR, M.R.C.P.Ed., and J. J. R. DUTHIE, F.R.C.P.Ed. 1257

MEDICAL MEMORANDA

Xanthoma Palpebrarum and Cardiovascular Disease. P. P. MCKINNEY, M.B. 1259

Acute Volvulus of the Stomach. P. QUINET, F.R.C.S.Ed. 1259

REFRESHER COURSE

Menstrual Disorders and the Menopause—II. P. M. F. BISHOP, D.M. 1268

GENERAL ARTICLES AND NEWS

Chemotherapy of Cancer 1271
THE SIR CHARLES HASTINGS LECTURE 1272
MEDICAL NOTES IN PARLIAMENT 1284
UNIVERSITIES AND COLLEGES 1286
MEDICAL NEWS 1288
BIRTHS, MARRIAGES, AND DEATHS 1290
QUESTIONS AND COMMENTS 1291

REVIEWS

Recent Pharmacology 1260
Radiography in Surgery 1260
Surgery for Students 1260
Psychology of Kretschmer 1261
Books Received 1261

OBITUARY

J. A. Murray, M.D., F.R.S. 1281
Alexander Low, M.D., LL.D. 1282
W. H. Steele, M.B. 1282
J. K. P. Clarke, M.B. 1283
Christopher Rolleston, M.D., M.R.C.P. 1283
H. Pomfret Kilner, M.B. 1283

Epidemiology Section 1287

LEADING ARTICLES

A Failing Policy 1262
Measuring Improvement in Rheumatoid Arthritis 1263

ANNOTATIONS

Paying the Doctor 1264
Rutherford Memorial 1265
Durham and the Doctors 1265
Treatment of the Maladjusted Child 1265
Higher Pay in Armed Forces 1266
Teething Troubles 1266
Proteins and the Clinician 1267

REPORTS OF SOCIETIES

ROYAL SOCIETY OF MEDICINE 1274

MEDICO-LEGAL

Death from Tetanus 1283

SUPPLEMENT

Proceedings of Council *221*
THE BRITISH MEDICAL GUILD *223*
Kingston Hospital Dispute—HOSPITAL EXPENDITURE—DISPLACED REGISTRARS *224*
PUBLIC HEALTH COMMITTEE *226*
PART-TIME NATIONAL SERVICE *227*
INDUSTRIAL INJURIES INSURANCE *227*
HEARD AT HEADQUARTERS *227*
ARMED FORCES MEDICAL OFFICERS *228*
NINTH ANNUAL GENERAL MEETING OF THE BRITISH MEDICAL STUDENTS' ASSOCIATION *229*
CORRESPONDENCE *230*
B.M.A. LIBRARY *232*
H.M. FORCES APPOINTMENTS *233*
ASSOCIATION NOTICES *233*

CORRESPONDENCE

Guy Fawkes Day—The Afterglow. W. GISSANE, F.R.C.S. 1275
Cost of Academic Clinical Office 1275
Displaced Registrars. I. ATKIN, M.D.; H. DONOVAN, F.R.C.S., and A. GOUREVITCH, F.R.C.S.; A. W. FOWLER, F.R.C.S.; D. WEITZMAN, M.D. 1276
Abnormalities in Developing Chickens. DENIS BROWNE, F.R.C.S. 1277
Dead Bodies in Water. W. B. PEACOCK, M.D.; H. WILLOUGHBY, M.R.C.S. 1277
Ring Round the Penis. M. DRURY, M.B., and K. MCKENZIE, M.B. 1278
Transfusion and Viral Hepatitis. F. O. MACCALLUM, M.D., and W. d'A. MAYCOCK, M.D. 1278
Haemolytic Streptococcal Gangrene Treated with Streptomycin. H. M. KARN, M.B. 1278
Unabsorbable Sutures. M. N. RANKIN, M.B. 1279
A Modified Skin Stitch. J. W. RIDDOCH, F.R.C.S.Ed. 1279
A Clip for Syringes. D. A. HERD, L.R.C.P.Ed. 1279
Orf in Man. A. K. RANKIN, M.B. 1279
Mass Radiography. THOMAS PAXON, M.B. 1279
Child Welfare—Past, Present, and Future. MATHILDA MENZIES, M.D. 1280
Factory Doctors in the Health Team. M. E. M. HERFORD, M.B. 1280
Teething. H. M. TIETZE, M.D. 1281
Wrong Use of Fenestration Operation. H. NORMAN-BARNETT, F.R.C.S.Ed. 1281
R.M.B.F. C. L. BATTERSON, M.R.C.S. 1281
Points from Letters 1281

BRITISH MEDICAL ASSOCIATION, TAVISTOCK SQUARE, LONDON, W.C.1

No. 4691, WEEKLY, PRICE 2/-

Copyright

REGISTERED AS A NEWSPAPER

CHEMOTHERAPY OF **TUBERCULOSIS** AND **LEPROSY**

Thiacetazone

Thiacetazone (para-acetylaminobenzaldehyde thiosemicarbazone) has received extensive clinical trial in Germany for the treatment of tuberculosis, and favourable results have been reported in pulmonary cases of the early exudative type and in tracheo-bronchial, laryngeal and intestinal tuberculosis. More recently, the drug has been shown to justify detailed examination in the treatment of leprosy. Under the trade name of 'Thioparamizone' it is available as tablets of 50mg. in containers of 100, 250 and 500.

HPL

Literature and prices available on application to
HERTS PHARMACEUTICALS LIMITED
WELWYN GARDEN CITY
G.M.59 ENGLAND

'THIOPARAMIZONE'
TRADE MARK BRAND

Thiacetazone

When they're 'all legs'

Suddenly the children start to look like young colts, they get through one pair of shoes after another . . . .
This is the age — the pre-teens — when buying Clarks Shoes is a particularly sound investment, not merely because of the supple and enduring leather but because of their *fit* — plus the extra space at the toes.
Clarks footgauge decides which of the four-widths-to-each-size is the child's 'own.' A well-fitting Clarks shoe does not "scuff," it keeps its heel-shape—in short, like any tailored garment, it lasts. And—even more important—the child's feet stay straight and strong.

Clarks
SHOES
Established 1825

Have you had your copy of

"SEVEN PILLARS OF PRACTICE"

— a helpful booklet available to all members of the medical profession?

If not, please write to

THE MEDICAL SICKNESS, ANNUITY & LIFE ASSURANCE SOCIETY, LTD.
7, Cavendish Square, London, W.1
(Tel.: LANgham 2992)
referring to this advertisement

1950

BRITISH MEDICAL JOURNAL

LONDON SATURDAY DECEMBER 2 1950

PROTEIN STRUCTURE AND CLINICAL PROBLEMS*

BY

E. C. DODDS, M.V.O., M.D., F.R.C.P., F.R.S.

Courtauld Professor of Biochemistry in the University of London; Harveian Librarian of the Royal College of Physicians

The proteins have always been an object of interest to chemists and biologists. Their investigation, however, was for long hampered by the old vitalistic ideas which regarded protoplasm as fundamentally living and therefore beyond the scope of the chemist. Despite the fact that as early as 1746 Beccari succeeded in isolating gluten from wheat flour, and in 1859 Ritthausen had developed methods for preparing vegetable proteins in a relatively pure and stable form, the attack on animal proteins was still held back by devotion to vitalism. The decisive blow to this old doctrine was struck by Hoppe-Seyler's crystallization of the protein haemoglobin in 1866. This achievement was followed by the crystallization of a number of other proteins of animal origin, culminating in the production of crystalline egg albumin in 1892 by Hofmeister.

Experimental clinicians and biologists have been mainly interested in proteins on account of their nutritional value. It was clearly recognized that, though all proteins provide necessary nitrogen in assimilable form, they differ among themselves in nutritional value, as shown classically by the work of Hopkins and his school, and this led to the concept of "essential amino-acids." Proteins are also important in determining water balance and the osmotic pressure of the blood, and there is an increasing recognition of their significance in immunity. But our whole conception of the structure of tissues in the body, and their relationship to the internal environment, has undergone a complete change since the introduction of labelled or tagged elements into the study of metabolism. Before the introduction of this new technique, proteins, and other tissue constituents such as minerals and so forth, were considered as being in more or less static equilibrium, and a protein molecule once made and stabilized stayed in its intact state in the plasma or tissue.

We now know from a study of the metabolism of amino-acids containing labelled or tagged elements that proteins are steadily being broken down and built up, and that the whole of the protein system of the body is in dynamic equilibrium with the amino-acid content of the tissue fluids and the blood serum. Schoenheimer, in his classical experiments (Schoenheimer *et al.*, 1939 ; Schoenheimer, 1942), has used deuterium and ^{15}N labelled amino-acids for the study of protein turnover *in vivo*. He showed that the half-life of liver proteins in the adult rat is seven days. Sprinson and Rittenberg (1949) were able to extend these investigations and to develop an elaborate quantitative method for studying nitrogen balance and protein synthesis in the rat. By the use of suitably labelled amino-acids it was possible to study what they termed the metabolic pool in both the rat and man and to work out the rate at which amino-acids were passed out of this metabolic pool into the body. Again, they showed that in the rat the half-life of the total proteins was about 17 days, of the liver, plasma, and internal organ proteins some 6–7 days, and of the total carcass proteins 21 days. In the case of man the total turnover of protein occurred in about 80 days, while the liver and serum proteins were turned over in 10 days and the lung, brain, bone, skin, and principally muscle in 158 days. Tarver and Reinhardt (1947) were able to make some similar observations by studying the metabolism of methionine containing ^{35}S in normal and hepatectomized dogs, and they showed that the incorporation of tagged methionine into body proteins could take place without the intervention of the liver. The administration of ^{35}S containing methionine resulted in a rapid increase in the concentration of radioactive sulphur in plasma proteins, the five-hour value being twice that at two hours. The intestinal mucosa surprisingly absorbed very large quantities of the labelled amino-acids, indicating that the intestinal mucous membrane must play an important part in protein synthesis. Extensive experiments in this field have shown that the injection of such amino-acids is followed by their very rapid uptake into the body proteins, particularly the proteins of the visceral organs. It would appear that from this storehouse the amino-acids are distributed for incorporation into other tissues. A full review of this fascinating subject is given in a recent paper by Borsook (1950).

From the constitutional point of view, clinician and biologist have been content up to the present with the knowledge that proteins are composed of amino-acids joined together through the classical CO–NH linkage. The proteins possess a very large number of amino-acids joined together in this manner, and therefore are bodies of high molecular weight. It stands to reason that, if the molecular weight can vary from 10,000 to 1,000,000 or over, the disposition of the peptide chains, or strings of amino-acids, must be of considerable importance. How, in fact, are these strings orientated in space? Are they long single chains, are they branched chains arranged in a definite manner, or are they just a jumble like a badly wound ball of string? This problem has fascinated physical and stereo-chemists from the very time that the peptide-linkage theory of protein structure was accepted.

As Dr. Dorothy Crowfoot Hodgkin (1949) points out, it is difficult to know whether it is wise at the present juncture to comment on protein structure or whether it would be better to wait until all the accurate analyses now being made throughout the world on protein crystals have been received and collated. There is no doubt that the greater accuracy of these methods of measurement has revealed

*An abridged version of the Bertram Louis Abrahams Lecture delivered at the Royal College of Physicians of London on July 13.

that none of the theories so far considered will stand up, and that we are driven to the conclusion that the protein molecule consists of relatively long chains of peptides strung together by various bridges and possibly coiled or wound round in order to give a compact mass. There seems to be enough evidence to show that proteins such as haemoglobin are composed of peptide chains which are folded on each other in the manner shown in Fig. 1.

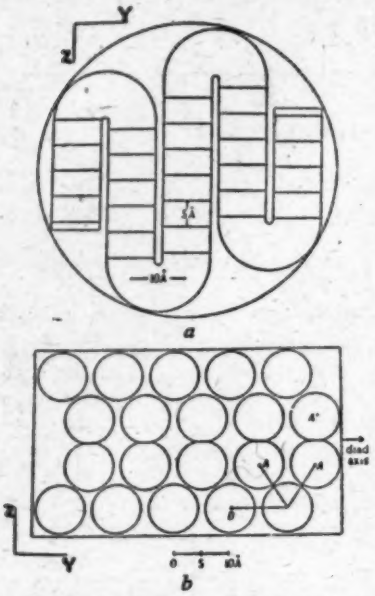


FIG. 1.—Suggested structure of haemoglobin. (*a*) Basal section showing folded polypeptide chain. (*b*) Vertical section showing packing. Taken from Perutz, *Proc. roy. Soc.*, A, 1949, 195, 474 (Fig. 23).

Astbury and Street (1931) have pointed out that proteins can be classified as of either the fibre or the globulin type. The fibre proteins consist of silk fibroin, myosin (from muscle), and keratin (skin and hair), while the globular proteins are those in which clinicians are primarily interested—namely, globulins, albumins, and so forth.

It is proposed to take the study of the insulin molecule as the typical example of this vast and complicated subject of the configuration of the protein molecule.

Protein Structure as Exemplified by a Study of Insulin

Physical Studies.—Gutfreund (1948) has shown that the molecular weight of insulin is 47,000–48,000 and that the variable results obtained in previous estimations were due to the existence of an equilibrium between the 48,000 molecule and four apparently identical submolecules of 12,000 weight each. Further support for the 12,000 subunit in insulin comes from the finding that it passes through "cellophane" impervious to molecules of weight 21,000 and higher values.

Analysis.—Chibnall's (1946) analysis shows that the 12,000 weight subunit of insulin probably contains 106 amino-acid residues, of which 101 have been accounted for. These are: aspartic acid 5, glutamic acid 15, glycine 7, alanine 6, valine 8, leucine and isoleucine 14, phenylalanine 6, tyrosine 9, serine 6, threonine 2, lysine 2, histidine 4, arginine 2, proline 3, half-cystine 12. The remaining five residues probably are accounted for as a cumulative error in the numerous analyses. Insulin lacks methionine and tryptophan, but still contains 16 different amino-acids, and in any case methionine and tryptophan are present only in very small amounts in all but exceptional proteins.

Insulin has a high proportion of sulphur, like the keratins and certain pituitary hormones, and the cystine apparently accounts for all the sulphur of insulin, though this has been the subject of much controversy in the past (for example, du Vigneaud, 1927). Scott (1934) found that the addition of zinc, nickel, cobalt, or cadmium alone among metallic cations is necessary for the crystallization of insulin.

Main Structural Arrangement.—The most important contributions to the structural theory of insulin have come from the laboratory of Professor Chibnall, at Cambridge. Early work indicated that there were a number of peptide chains in the insulin molecule, but it was not until 1945 that Sanger, working in his laboratory, was able to demonstrate that there were four chains in the insulin submolecule, two with glycine and two with phenylalanine residues providing the free end amino-groups of the chains. The view was held that these chains were probably joined together by six cystine disulphide bridges (Fig. 2), and this has been substantiated by Sanger (1948, 1949). If these bridges are broken the separate chains can be fractionated with ammonium acetate into two distinct groups, A and B. The A fraction is obtained from the glycine chains of insulin, and each chain has a molecular weight of about 2,500 and four cysteic acid residues. The B chains contain all the lysine, histidine, arginine, phenylalanine, proline, and (in the case of bovine insulin) all the threonine of the insulin submolecule, so that the two types of peptide chain in insulin are very different in structure.

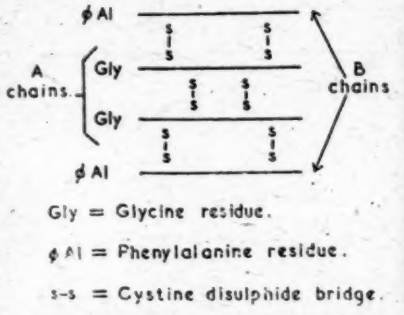


FIG. 2.—Showing the six cystine disulphide bridges joining the four chains of the insulin submolecule.

In bovine and ovine insulins the A fractions contain glycine, alanine, valine, leucine, isoleucine, tyrosine, serine, cystine, aspartic acid, and glutamic acid only, whereas porcine insulin A chains have been found to contain some threonine also (Sanger, 1949).

Amino-acid Sequences.—Sanger has obtained by analysis a series of peptides which leave no doubt that part of the amino-acid sequence is: in the A chains (amino-group of glycine terminal and free) glycyl-isoleucyl-valyl-glutamyl-glutamyl-, and in the B chains (amino-group of phenylalanine terminal and free) phenylalanyl-valyl-aspartyl-glutamyl. Some of the aspartic and glutamic residues are in the form of their amides (that is, asparaginyl and glutaminyl residues). An internal sequence in the B chains was also determined by the labelling of the ε-amino group of the lysine side-chains. This sequence was: threonyl-prolyl-lysyl-alanine. This is of especial interest since threonine, proline, and lysine are among the rarest amino-acids in the insulin submolecule.

Enzymic Studies

Butler *et al.* (1948, 1949, 1950) have employed crystalline trypsin, chymotrypsin, and pepsin on crystalline insulin. Trypsin was found to have only a very slight action, if any, on the protein. This is in accord with the very low lysine and arginine content of the hormone (two residues of each per submolecule); these amino-acids must be present in synthetic peptides before trypsin can exercise its hydrolytic action on them (Bergmann and Fruton, 1937 : and later).

Chymotrypsin and pepsin both readily degrade insulin to peptides of unequal sizes. In both cases a large fragment of weight 4,000–5,000 is produced from each submolecule, and the rest appears as smaller trichloroacetic-acid-soluble peptides of average size tetra- or hexa-peptide, though there is evidence that one of these soluble peptides derived from the chymotryptic fission of insulin is as large as 2,000 in molecular weight.

The large precipitable fragments have been called the "core" of the insulin submolecule, since they have three or four of the six cystine disulphide bridges and, compared with insulin, are relatively resistant to digestion. The free amino-groups of the core formed by chymotryptic action (containing parts of the four original peptide chains of insulin) are those of glycine, valine, and leucine (insulin has glycine and phenylalanine).

Physical measurements on the insulin core (electrophoretic diagram by Dr. J. M. Creeth and diffusion and sedimentation by Dr. K. Pedersen at Upsala) have shown that it is in all probability a single substance of molecular weight about 5,000, whereas the core formed by the action of pepsin is inhomogeneous, the smaller material having a molecular weight of about 4,000. An intensive study of the composition of these fractions produced by enzymic action is being undertaken at the Courtauld Institute.

Many of these structural details from the work described above can be shown together in diagrammatic form. In the diagram below, amino-acids are indicated by abbreviations, and one submolecule of insulin (weight 12,000) is illustrated (Fig. 3). It has been assumed that the two "glycine" chains are alike and the two B chains also alike. The positions of the histidine (Hist) and arginine (Arg) residues and the threonine, proline, lysine, alanine sequence are not known, but they lie within the B chains. The core formed by the action of chymotrypsin is shown by the enclosed portion, since it is known to have four cystine bridges, glycine and valine (and also leucine, not shown) terminal acids, two histidine residues, four tyrosine residues, and 0 or 1 phenylalanine residue per weight of 5,000, a weight corresponding to about 45 residues. The true positions of the cystine disulphide bridges (–SS–) are unknown. The tyrosine and phenylalanine residues other than those designated by Ty or ϕAl are given as A, and these have been distributed throughout the extra-core part to conform with the fission of the molecule at these points into small peptides of average size about penta-peptides. It is not certain from the work of Lens (1948) that alanine (Al) lies at the carboxyl end of every peptide chain, as shown here.

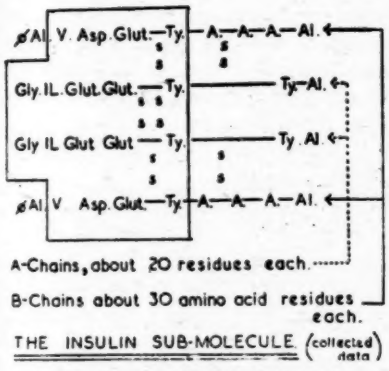

øAl. V. Asp. Glut.—Ty.—A.—A.—A.—Al.
Gly. IL. Glut. Glut.—Ty.
Ty.—Al.
Gly IL Glut Glut—Ty.
Ty. Al.
øAl. V Asp. Glut.—Ty.—A.—A.—A.—Al.
A-Chains, about 20 residues each.
B-Chains about 30 amino acid residues each.
THE INSULIN SUB-MOLECULE (collected data)

FIG. 3.—Key to abbreviations: øAl = phenylalanine; V = valine; Asp = aspartic acid; Glut = glutamic acid; Gly = glycine; IL = Isoleucine; Ty = Tyrosine; A = aromatic amino-acid residue (phenylalanine or tyrosine); –SS– = cystine disulphide linkage.

As all this information is far in excess of that available for any other protein it is too early to say how representative of proteins in general it is, but there is no reason to suppose that it is not so.

Biological Activity of Insulin

The source of the activity of insulin remains unknown. Chemical studies have provided the most useful information on this point. A paper by Fraenkel-Conrat and Fraenkel-Conrat (1950), re-examining much previous work, concludes that the cystine disulphide bridges, the carboxyl groups, and about half of the tyrosine phenolic hydroxyl groups are essential for the activity. The aliphatic hydroxyl, the imidazole, amide, and guanidyl groups appear to be dispensable.

No fragment of insulin provided by enzymic degradation with crystalline pepsin or chymotrypsin or by crude pancreatin or papain has shown any activity, whereas crystalline trypsin does not attack the protein and the activity is retained.

It is not possible to say definitely, however, whether the activity resides in a part or in the integrity of the whole molecule, for the enzymic degradations are not random processes and they may all involve fission within an active grouping (if such exists). In the enzyme inactivation quoted above, the loss of activity is approximately proportional to the loss of intact protein.

Other Protein Hormones

It must be clearly recognized that the account given of the structure of insulin is only the very barest outline of the vast amount of work in progress on this one protein. A description has been given in the hope that the magnitude of the task of determining the constitution of a single protein may be appreciated. Not only has the number of chains, etc., to be determined, and the number of amino-acids in each chain, but also the order in which they are arranged.

A number of other protein hormones await investigation. All the hormones of the anterior lobe of the pituitary are of a protein character. Many of them have been isolated as chemically pure proteins, but up to the present little or no work has been done on their configuration. The investigator is severely handicapped by the scarcity and great expense of pituitary hormones, and it may well be a considerable time before our knowledge of such bodies as the growth hormone, lactation hormone, and the gonadotropic factors can be brought up to the same standard as that of insulin. Should the importance of these hormones require any stressing, it would only be necessary to refer to the overwhelming clinical interest in the adrenocorticotropic hormone at the present moment. Until comparatively recently this hormone was known only to experimental biologists, endocrinologists, and biochemists, but to-day, in its abbreviated form of A.C.T.H., its name is on every clinician's tongue.

Recent work at the Mayo Clinic has shown that the injection of this hormone into patients with rheumatoid arthritis will produce an astonishing remission of symptoms. From the protein chemist's point of view one of the most interesting developments has arisen through the work of Li (1949), who has shown that it is possible to produce by peptic hydrolysis a low-molecular-weight fragment possessing all the activity of the intact protein. It would appear that this low-molecular-weight substance is a peptide containing 6, 7, or 8 amino-acids.

The work of Morris and his collaborators (Cortis-Jones, Crooke, Henly, Morris, and Morris, 1950) has indicated that this low-molecular-weight substance may be present in active preparations of the whole proteins even without prior hydrolysis. Morris and his collaborators have shown that it is possible to separate the clinically active low-molecular-weight fraction from inactive A.C.T.H. protein by ultrafiltration. It is obvious that if the constitution of the peptide can be determined its synthesis will go a long way towards solving the problems of the "A.C.T.H.–cortisone" situation.

During our work on insulin in the Courtauld Institute we have always hoped to find an active fraction, and the

search for such a substance still goes on despite the fact that we have so far had no success.

It will not be necessary to point out that the synthesis of proteins is at present quite out of the question. Great advances have been made in the synthesis of polypeptides, and there now exist simple and economical methods of making these substances in the laboratory. This has been reviewed recently (Dodds, 1950).

Proteins of Toxic Agents

That, in certain circumstances, proteins can act as highly toxic substances has been known for a very long time. The death produced by anaphylaxis is a well-known phenomenon and is associated with the injection of proteins. Vaughan and his co-workers (1913) showed that it was possible, by treating harmless proteins with dilute alkalis, to produce highly toxic substances capable of causing an immediate and sometimes fatal fall of blood pressure when injected into animals.

This was regarded as an entirely academic subject, and received very little attention until Sir Edward Mellanby (1946) produced his startling work on canine hysteria. Briefly, Mellanby was able to show that hysteria can be produced in dogs whose diet consists of some 60% of bread made from flour which has been subjected to a process known to the milling industry as "improvement." It has been known for over a century that flour, when stored for long periods, would give a loaf of a lighter character and better texture than one made from flour freshly milled. The storage of flour is an uneconomical procedure, and cereal chemists therefore studied the nature of this ageing problem and were able to develop methods of treating flour in order to age it artificially. Most improvers are oxidizing agents, but one of the most popular and convenient is gaseous nitrogen trichloride, used in the "agene process." Not only is the flour "improved" by this treatment, but it is simultaneously bleached. It is certainly safe to say that over 90% of the flour of Great Britain and the United States has been subjected to this treatment. Despite the fact that there has been official uneasiness about improvers ever since their introduction, it is again safe to say that any immediate danger from the treatment never entered anybody's head, official or otherwise.

To return to the experiments of Mellanby, he was able to prove conclusively that only those dogs fed on bread made from agene-treated flour suffered from hysteria. The control dogs fed on identical flour, but untreated, remained perfectly healthy and free from symptoms. This publication by Mellanby, and the showing of his film on hysteria, caused a profound sensation in nutritional circles, and also among millers and legislators.

Moran and his colleagues (Bentley *et al.*, 1950) at the Research Association of the British Flour Millers were able to prove that the agene process attacked the protein of the flour, and that powerful toxic hysteria-producing substances could be formed by the treatment of gluten with agene. Further, this toxicity could be induced not only in flour but also in such inert proteins as casein and zein; and in a brilliant series of papers from Moran's laboratory the whole nature of the process has been elucidated. Thus the toxic fraction has been concentrated and finally obtained in crystalline form, and later its constitution and synthesis have been worked out.

As the result of this work an entirely new approach to the activity of the central nervous system has been provided, and from the academic point of view a detailed study of compounds in the series of those produced in the laboratories at St. Albans should prove of very great interest.

It can thus be seen that proteins used for food can be turned into highly toxic substances, at least for animals, by processes which have been regarded for decades as quite harmless. We are not concerned here with the clinical implications of this work, but it is perhaps reassuring to be able to say that up to the present, even with enormous intakes of highly agenized flour, no toxic symptoms have been detected in the human subject.

Bacteriological Toxins

The exotoxin produced by Type A *Clostridium botulinum* forms an example of the group of bacterial toxins of very high lethal power. Like diphtheria and tetanus toxins, botulinus toxin has now been isolated and crystallized (Lamanna, McElroy, and Eklund, 1946; Abrams, Kegeles, and Hottle, 1946). Physico-chemical characterization by electrophoresis, sedimentation, diffusion, and viscosity measurements (Putnam, Lamanna, and Sharp, 1946, 1948; Kegeles, 1946; Abrams, Kegeles, and Hottle, 1946) has shown it to be a single homogeneous heat-labile protein with the solubility properties of a globulin. Serological data also show that the toxin acts as a single substance (Lamanna and Doak, 1948).

All the three toxins referred to have somewhat spectacular potencies, but botulinus toxin is the most potent by a considerable margin, and is indeed the most poisonous substance known. Some comparative data are as follows:

Toxicities of Purified Bacterial Toxins (in Terms of Minimum Lethal Dose for 20-g. Mouse; data from Pappenheimer, 1947)

Diphtheria	175 MLD per mg. toxin
Tetanus	10×10^6 MLD per mg. toxin
Botulinus	30×10^6 MLD per mg. toxin

These high potencies are of great biochemical interest when the possible modes of action of the toxins are considered. In this respect botulinus toxin is outstanding when its toxicity is examined on a molecular basis, as its molecular weight is about 1,000,000 (Putnam, Lamanna, and Sharp, 1946; Kegeles, 1946), compared with values of approximately 70,000 for the other toxins. Accordingly, it may be calculated that the lethal dose for a mouse contains only 20,000,000 molecules: toxaemia may thus be produced at a dosage level of one molecule per cell, and even at this concentration only a relatively small proportion of the tissue can actually be affected.

It is now established that the toxicity of the pure crystalline toxin is 220×10^6 LD50 per mg. nitrogen for 20-g. mice, or approximately 30×10^6 LD50 per mg. toxin. Calculated on a weight basis, it follows that the LD50 for a 75-kg. man would be 1.2×10^{-7} g., or only 0.12 μg. Alternatively, it has been computed (Pappenheimer, 1947) that 1 mg. of the toxin would be sufficient to kill more than 1,000 *tons* of guinea-pig. Considering the figure for a man again, if one takes the proportion of water in the body as 85% one may calculate that a toxin concentration of approximately 2×10^{-12} g./ml. of total body water would be lethal in 50% of cases. This figure is even more impressive when the high molecular weight of the toxin (1×10^6) is taken into account; thus the lethal concentration of toxin within the body is only 2,000 molecules per ml. of total water.

First culture of the organism gives solutions of approximately 1×10^6 LD50 (mouse) per ml. Of such a solution (which might be compared with spoilt food) only 0.04 ml. would be required for a fatal dose for a man. Botulinus toxin, moreover, is unique among the bacterial toxins in that it is active by mouth.

It is difficult to visualize any direct mechanism whereby such a small number of molecules can cause death, and

it has been suggested (Pappenheimer, 1947) that the toxin acts not by inhibiting an enzyme action, nor by acting as an enzyme itself, but rather by blocking the synthesis of an essential enzyme. Other workers (Putnam, Lamanna, and Sharp, 1948) have speculated on the enzymatic synthesis of a cellular poison from some normal metabolite. Characteristic of its action, as also of diphtheria and tetanus toxin, is the latent period before the onset of symptoms, the time being roughly inversely proportional to the logarithm of the dose. The suggestion (Guyton and MacDonald, 1947) that this period is associated with the slow diffusion to be expected of a large molecule may be discounted, as Burgen, Dickens, and Zatman (1948) have shown that the latent period and duration of paralysis are prolonged by lowering the temperature to an extent much greater than would be accounted for on a purely physical basis. Death generally occurs within two or three days of the onset of symptoms and is due to respiratory paralysis.

The pharmacology of the toxin has been investigated by many workers (for example, Edmunds and Long, 1923; Dickson and Shevky, 1923; Bishop and Bronfenbrenner, 1936; Guyton and MacDonald, 1947), and it has been established that the site of action is at the neuromuscular junction. In an investigation of the various factors involved in the paralysis, Burgen, Dickens, and Zatman (1948) utilized the isolated rat phrenic nerve diaphragm preparation of Bülbring (1946). It was shown that conduction in the nerve was unaffected by the paralysis, and that the block differs from that produced by curare in that motor nerve tetani are maintained. Diaphragms from rats actively immunized with toxoid were not affected by the toxin.

The oral toxicity of the substance has often been correlated with the reported resistance to proteolytic enzymes (Pappenheimer, 1947, 1948; Putnam, Lamanna, and Sharp, 1948), though the problem is then raised of how such a large molecule could be absorbed through the wall of the gut. Such resistance, however, is not well established, as so much of the work on which this conclusion was based was done on very impure toxin preparations.

The preparation of the pure crystalline toxin by the American workers has raised the possibility of new approaches to the problem of the mode of action, and investigations have been started both in this country and in the U.S.A. Already the toxin has been characterized by a complete elemental and amino-acid analysis (Buehler, Schantz, and Lamanna, 1947), but this gave no clue to its action, no abnormal amino-acid nor characteristic toxic grouping being revealed.

In this country, work has been designed to establish whether the toxin is, in fact, resistant to proteolytic enzymes and, if not, whether a toxic fragment may be split off the main molecule by such treatment. The experiments of Li and of Morris and his colleagues, already referred to, would lend a certain amount of support to the possibility that some active fraction may be split off the molecule.

The investigation is complicated by the fact that the initial culture of the organism results in a very low concentration of the toxin and the subsequent working-up tends to be rather long and involves too many precipitation steps, to which the toxin is peculiarly sensitive. Investigations on the possible utility of the modern methods of separation by electrophoresis and of concentration by ultracentrifugation are at present in hand.

Virus Proteins

The bacterial toxins mentioned in the previous section are, relatively speaking, straightforward protein poisons, though we have really no knowledge of their mode of action. An entirely different type of toxic protein has been discovered in the plant virus diseases. Largely due to the work of W. M. Stanley (1940, 1943), the causative agents of certain plant diseases, such as tobacco plant disease, bushy stunt disease, and similar conditions, have been found to be of a protein character. Stanley and his colleagues have actually prepared crystalline specimens of a number of these substances. If a plant is injected with a small quantity of these crystals, the disease will be reproduced in the plant, and analysis of the infected plant will at a later date show a great increase in this crystalline material, and we have the paradoxical phenomenon of an infective agent in crystalline form apparently reproducing itself.

At present there is no adequate explanation for this, but it would certainly be a most reasonable assumption that the crystalline protein alters the synthetic process of the cells of the plant so that they continue to produce more of this crystalline protein, and that this in turn produces the outward and visible signs of the disease.

These crystalline protein viruses have been analysed for their amino-acid content, and work is at present being conducted on a number of them in the same manner as described for insulin. It has been shown that by passage through various plants the virulence of these crystalline substances can be varied and that the variation is accompanied by a change in the chemical constitution of the protein. We do not know as yet whether the viruses of human and animal diseases such as rabies and yellow fever and so forth belong to the same family as the plant viruses, but we do know that it is possible to alter their virulence and activity by passage. An immediate classical example is the work of Pasteur on rabies and the work on yellow-fever virus. This modification of the protein structure of plant viruses leads to the question of immunity.

It is now well known that the immune bodies circulating in the blood and body fluids consist of modified globulins. The constitution of these globulins is at present unknown, and only intensive work like that on insulin will solve the differences between the immune body globulins and the normal serum globulins. When one thinks of the complexity of the insulin molecule, and when one bears in mind the fact that proteins are continuously being destroyed and built up again in the body, it becomes a matter of wonderment and astonishment that the injection of an antigen on two or three occasions will produce immunity in the animal body, lasting in some cases for a period of years and in others apparently for a lifetime, as in the case of yellow fever. What is the mechanism that teaches the cells to alter the constitution of the globulins synthesized by them so that immune bodies will be produced and, moreover, continue to be produced for years? Again, it is possible only to speculate on this, and we can only adopt the hypothesis supported by Burnet and Fenner (1949), and known as the self-marker theory, that the antigen remains for a very long period in the body cells capable of producing antibodies, and that the antigen acts on the cells so that they synthesize the immune globulins.

Conclusion

I trust that I have succeeded in indicating that this vast problem must be of immediate importance to anyone concerned with the investigation or treatment of disease. When one contrasts the great complexity of the protein molecule with the fact that millions of these substances are continuously being built up and disintegrated in the human

body, and moreover rebuilt to precisely the same structure, one cannot help but speculate about the controlling mechanism. It is rather a terrifying thought that the whole of the protein in the human body is replaced in roughly 160 days, and at the present time we can only speculate on the mechanism controlling this elaborate resynthesis, where even a single amino-acid must not be out of place if the hormone is to have its activity or the antibody its potency.

It might well be that, when the mechanism of perhaps the most complex problem in human biochemistry is understood, we shall find the answer to many problems, possibly even the mechanisms of senescence and of cancer.

I should like to express my thanks to the President and Censors of the Royal College of Physicians for the honour of giving the Bertram Louis Abrahams Lecture, and my deep appreciation of the help given to this work and the preparation of the lecture by Professor A. C. Chibnall, F.R.S. It is a pleasure also to record the great assistance given me by Dr. D. N. Baron and by my colleagues in the Courtauld Institute who work on the proteins—Dr. J. M. Creeth, Dr. D. M. P. Phillips, Mr. P. A. Charlwood, and Dr. Joan Stephen.

REFERENCES

Abrams, A., Kegeles, G., and Hottle, G. A. (1946). *J. biol. Chem.*, **164**, 63.
Astbury, W. T., and Street, A. (1931). *Philos. Trans.*, A, **230**, 75.
Bentley, H. R., McDermott, E. E., Pace, J., Whitehead, J. K., and Moran, T. (1950). *Nature, Lond.*, **165**, 150.
Bergmann, M., and Fruton, J. S. (1937). *J. biol. Chem.*, **118**, 405.
Bishop, G. H., and Bronfenbrenner, J. J. (1936). *Amer. J. Physiol.*, **117**, 393.
Borsook, H. (1950). *Physiol. Rev.*, **30**, 206.
Buehler, H. J., Schantz, E. J., and Lamanna, C. (1947). *J. biol. Chem.*, **169**, 295.
Bülbring, E. (1946). *Brit. J. Pharmacol.*, **1**, 38.
Burgen, A. S. V., Dickens, F., and Zatman, L. J. (1948). *J. Physiol.*, **109**, 10.
Burnet, F. M., and Fenner, F. (1949). *Production of Antibodies*, 2nd ed. Macmillan, Melbourne.
Butler, J. A. V., Dodds, E. C., Phillips, D. M. P., and Stephen, J. M. L. (1948). *Biochem. J.*, **42**, 116.
—— —— —— —— (1949). Ibid., **44**, 224.
—— Phillips, D. M. P., Stephen, J. M. L., and Creeth, J. M. (1950). Ibid., **46**, 74.
Chibnall, A. C. (1946). *J. int. Soc. Leather Trades Chemists*, **30**, 1.
Cortis-Jones, B., Crooke, A. C., Henly, A. A., Morris, P., and Morris, C. J. O. R. (1950). *Biochem. J.*, **46**, 173.
Dickson, E. C., and Shevky, R. (1923). *J. exp. Med.*, **37**, 711.
Dodds, E. C. (1950). *Chem. & Ind.*, No. 8, p. 135.
Edmunds, C. W., and Long, P. H. (1923). *J. Amer. med. Ass.*, **81**, 542.
Fraenkel-Conrat, J., and Fraenkel-Conrat, H. (1950). *Biochim. biophys. Acta, Amst.*, **5**, 89.
Gutfreund, H. (1948). *Biochem. J.*, **42**, 544.
Guyton, A. C., and MacDonald, M. A. (1947). *Arch. Neurol. Psychiat., Chicago*, **57**, 578.
Hodgkin, D. Crowfoot (1949). *Cold Spring Harbor Symposia on Quantitative Biology*, **14**, 65.
Kegeles, G. (1946). *J. Amer. chem. Soc.*, **68**, 1670.
Lamanna, C., and Doak, B. W. (1948). *J. Immunol.*, **59**, 231.
—— Eklund, H. W., and McElroy, O. E. (1946). *J. Bact.*, **52**, 1.
—— McElroy, O. E., and Eklund, H. W. (1946). *Science*, **103**, 613.
Lens, J. (1948). *Biochim. biophys. Acta, Amst.*, **2**, 76.
Li, C. H. (1949). *Abstracts of Communications*, 1st International Cong. Biochemistry, p. 386.
Mellanby, E. (1946). *British Medical Journal*, **2**, 885.
Pappenheimer, A. M. (1947). *Fed. Proc.*, **6**, 479.
—— (1948). *Advances in Protein Chemistry*, **4**, 123.
Putnam, F. W., Lamanna, C., and Sharp, D. G. (1946). *J. biol. Chem.*, **165**, 735.
—— —— —— (1948). *J. biol. Chem.*, **176**, 401.
Sanger, F. (1945). *Biochem. J.*, **39**, 507.
—— (1948). *Nature, Lond.*, **162**, 491.
—— (1949). Ibid., **164**, 529.
Schoenheimer, R. (1942). *The Dynamic State of Body Constituents*, 2nd ed. Harvard U.P., Cambridge, Mass.
—— Ratner, S., and Rittenberg, D. (1939). *J. biol. Chem.*, **130**, 703.
Scott, D. A. (1934). *Biochem. J.*, **28**, 1592.
Sprinson, D. B., and Rittenberg, D. (1949). *J. biol. Chem.*, **180**, 715.
Stanley, W. M. (1940). Ibid., **135**, 437.
—— (1943). *Virus Diseases*. Cornell University Press.
Tarver, H., and Reinhardt, W. O. (1947). *J. biol. Chem.*, **167**, 395.
Vaughan, V. C., Vaughan, V. C., jun., and Vaughan, J. W. (1913). *Protein Split Products in Relation to Immunity and Disease*. Lea and Febiger, Philadelphia and New York.
Vigneaud, V. du (1927). *J. biol. Chem.*, **75**, 393.

REGULATION OF SECRETION OF CORTICAL HORMONES*

BY

MARTHE VOGT, M.D., Ph.D.

(From the Department of Pharmacology, University of Edinburgh)

There are several reasons why information about the control of the rate of secretion from an endocrine gland may be of interest. One is theoretical: an understanding of the factors regulating glandular activity gives us an insight into the part the gland plays in keeping up the *milieu intérieur*. The others are practical. First, in substitution therapy, such knowledge enables us to adapt the quantity of administered hormone to the requirements of the patient, as these vary with the circumstances. Secondly, in trying, for therapeutic reasons, to enhance or inhibit the action of a normal endocrine gland we have to know the conditions which will produce the desired effects on the gland.

Before discussing the information at present available about the control of adrenocortical activity, let me remind you of two fundamental facts concerning the physiology of the adrenal cortex. First, the gland, though secreting continuously, contains practically no stores of the biologically active hormones (Vogt, 1943), and, if synthesis were stopped while secretion were allowed to proceed at a normal speed, would lose its total hormone content in about 6–12 seconds. This means that synthesis is proceeding without interruption in the living condition, and explains the gland's large blood flow and high oxygen consumption. Secondly, the adrenal cortex has no secretory nerves, so that any nervous control over its activity would have to be exerted indirectly.

Experimental Methods

The knowledge we have of the control of adrenocortical secretion is almost entirely derived from animal experiments. A few introductory words on methods will be necessary. All available methods have their uses and their limitations, and the best picture of the gland's performance will be obtained by combining the information each of those methods can provide.

The oldest method is that which determines the experimental conditions which lead to hypertrophy of the cortex. It is suited to the investigation of all stimuli which can be applied over prolonged periods.

For stimuli of short duration suitable methods are the histological or chemical (Sayers *et al.*, 1945) determination of adrenal lipids, cholesterol, or ascorbic acid. Any acceleration of cortical secretion is reflected by an initial depletion in adrenal lipid or ascorbic acid usually followed by a restoration of the stores. This restoration may occur even if the accelerated secretion is maintained, either by prolonged action of the same stimulus or by a new one. Thus depletion is, as a rule, a sign of increased cortical secretion, while full stores of lipid or of ascorbic acid may be found in the later phases of increased activity as well as in the resting condition. Errors in interpretation may therefore arise if these methods are used in the investigation of prolonged or multiple stimuli.

Finally, cortical secretion may be measured directly by assaying adrenal venous blood for its hormone content (Vogt, 1943). The main use of this method is in acute experiments on anaesthetized animals or in perfused glands.

*Lecture delivered in the Department of Pharmacology, Oxford University, on October 23.

It has the advantage of providing at least a rough quantitative estimate of hormone production. Also, the interpretation of the results does not depend on the preceding history of the gland.

The Actions of A.C.T.H.

What have these different methods taught us? From the work on adrenal hypertrophy it has been known for a long time that innumerable conditions, usually but not always of a noxious character, stimulate the adrenal cortex. These conditions of "stress" include the action of infections, toxic substances, hormones, abnormal environmental temperatures, high altitude, exercise, haemorrhage—in other words, conditions which will increase the metabolic demands on either the whole body or some of its organs. The most important feature about this action of stress on the adrenal is that, in the mammal, it is abolished by hypophysectomy. The pituitary hormone released by stress and responsible for the adrenal hypertrophy is the "adrenocorticotrophic hormone" of the anterior lobe, or A.C.T.H. The actions of A.C.T.H. are twofold: (1) it maintains the normal size and structure of the adrenal cortex; and (2) it accelerates cortical secretion whenever stress is applied. This action, as shown on the perfused gland, occurs within a few minutes at the latest, and possibly instantaneously.

Since A.C.T.H. is so important for the activity of the adrenal cortex, we need to know how exclusively adrenal cortical function and adaptation of that function to variations in the requirements of the body depend on the pituitary. Obviously, some cortical function persists in the absence of the anterior lobe, or else hypophysectomy would be fatal.

Sections through the adrenal of hypophysectomized mammals show that the atrophy which follows the operation does not affect all zones of the cortex; the outer zone, or zona glomerulosa, is spared, or is possibly even larger than usual. As it is a sound biological argument that structurally different parts of an organ differ in their function, we may assume that, in the hypophysectomized mammal, certain functions of the adrenal cortex will be better preserved than others. There is indeed much circumstantial evidence that the electrolyte metabolism of the hypophysectomized animal is less impaired than that of the adrenalectomized animal. Carbohydrate, fat, and protein metabolism, however, with either procedure, are affected in about equal degree. Generalizations on this subject are, however, dangerous, as there are great species differences in the hypophysial–adrenal relationship. This is well illustrated by the fact that certain kinds of stress which no longer cause cortical hypertrophy in the hypophysectomized rat continue to do so in the hypophysectomized pigeon (Miller and Riddle, 1942).

The next question is whether this function can still be adjusted to the varying demands of the tissues. In the absence of any nervous innervation, any such regulation of the rate of cortical secretion must be mediated humorally by changes in the composition of the blood.

Blood Constituents Other than A.C.T.H.

Are there any blood constituents, other than A.C.T.H., which modify the rate of adrenal secretion? The perfused isolated adrenal of the dog has been used to investigate this problem. On that preparation a number of physiologically occurring substances were tested for their possible influence on the rate of cortical secretion.

Only two means were found to increase the rate of hormone production of the isolated adrenal preparation. One was the injection of adenosine-triphosphate (A.T.P.) and related compounds, and the other an increase in plasma potassium. A.T.P., when injected into the perfusion cannula, caused a short outburst of enhanced secretion. We know that substances carrying high-energy phosphate bonds enter into the metabolism of most cells, and experiments on the speed of uptake of ^{32}P (Gemzell, 1948) have shown that the adrenal gland is no exception, and also that its ^{32}P uptake is accelerated by A.C.T.H. The perfusion experiments suggest that these phosphates take part in the synthesis of cortical hormones. Normally they are not carried to the gland by the blood stream but are synthesized *in situ*.

The acceleration of cortical secretion by increasing the potassium content of the perfusing blood was obtained with or without simultaneous lowering of the plasma sodium. The alteration in plasma levels had to be of such a magnitude as would be expected to occur only in adrenalectomized dogs. The present methods of hormone assay are not sensitive enough for a decision whether a similar but smaller acceleration would occur if the changes in plasma electrolytes were within physiological range. If that were so, we would conclude that the regulation of cortical secretion which meets the demands of the electrolyte metabolism is entirely independent of pituitary action. It may, however, be that the direct stimulation of the adrenal cortex by excess potassium is an emergency mechanism reserved for pathological conditions only.

Causes of Changes in Pituitary Activity

We come now to the second part of our considerations. If the lion's share of control of cortical secretion is contributed by the pituitary, what, in turn, causes the necessary changes in pituitary activity? There we are still on insecure ground. We do not know whether it is the same factor which acts on the pituitary in all conditions of stress or whether there are several different factors. Two suggestions have, so far, been made for a possible common denominator of all conditions of stress which release A.C.T.H. The first one makes adrenaline responsible (Long, 1947) and is attractive for two reasons: first, adrenaline is undoubtedly secreted during many conditions of stress; secondly, the effect of adrenaline in accelerating cortical secretion is very striking. Infusions of "physiological" quantities of adrenaline—that is, quantities which may be released *in vivo* through prolonged stimulation of the splanchnic nerves—increase cortical secretion immediately, considerably (by many times the basal value), and for a period long outlasting its vascular effects (Vogt, 1944).

The site of action appears to be complex, an important factor being the release of A.C.T.H. This acceleration of cortical secretion by adrenaline constitutes an indirect control of the central nervous system over the function of the adrenal cortex. Is it all we require in order to explain the release of A.C.T.H. in stress?

Such a hypothesis can easily be put to the test, and experiments show that it is untenable. Two groups of rats are submitted to stress, the adrenals of one group having previously been denervated. Both groups of animals show a cortical response to stress—in other words, release A.C.T.H.—whether the method used for measuring the adrenal response be depletion of cortical lipids (Vogt, 1947) or of adrenal ascorbic acid. With the latter method, which gives quantitative data, we can analyse the matter further. Rats with denervated adrenals show the same fall in adrenal ascorbic acid after an injection of insulin as their normal controls. This shows that adrenaline is not indispensable for a response of the pituitary to stress, though it does not mean that adrenaline

plays no part in that response. On the contrary, the rats with denervated adrenals which have been given insulin in a dose well tolerated by normal rats are severely hypoglycaemic, comatose, or convulsing, so that we are in fact submitting the denervated animals to a much severer test instead of observing them and their controls under comparable conditions of stress. Equal depletion of adrenal ascorbic acid may actually constitute a diminished responsiveness of the denervated rat which is able to mobilize its A.C.T.H. only through the hypoglycaemia and not through the secretion of adrenaline as well. The results obtained on rats with denervated adrenals were confirmed in rats completely deprived of both adrenal medullae.

The second suggestion for a common factor releasing A.C.T.H. under all conditions of stress has been made by Sayers and Sayers (1947). Their hypothesis is as follows: in stress there is accelerated utilization of cortical hormones by the tissues, and therefore a low blood level of these hormones. This low level acts as a stimulus to the pituitary, which releases A.C.T.H. Conversely, output of A.C.T.H. is repressed when the level of circulating cortical hormones is high. This has been proved experimentally (Ingle, 1938; Sayers and Sayers, 1945) by showing that injection of cortical hormone inhibits the secretion of A.C.T.H. during stress. The stimulating effect of lack of hormone is much more difficult to demonstrate and has, so far, not been established.

Though we can be certain, therefore, that increased availability to the tissues of cortical hormones will check adrenocortical activity, we cannot be sure that lack of hormone will increase it by causing secretion of A.C.T.H. At present, however, this view is at least a good working hypothesis. It raises a number of further questions: is a low level of circulating cortical hormones the only stimulus which will induce the pituitary to give off A.C.T.H.? How does the role of adrenaline fit into the picture? Does it, too, like other forms of stress, act by increasing the utilization of cortical hormones in the tissues? Further, where are the receptors sensitive to low levels of circulating cortical hormones? Sayers and Sayers pictured them in the anterior lobe itself. For emotional stimuli, however, and for adrenaline, the work of de Groot and Harris (1950) and of Hume and Wittenstein (1950) suggests receptors in the hypothalamus. Does the whole control of A.C.T.H. secretion lie in the hypothalamus? To all these questions we can only guess the answers. And rather than by speculating, I should like to end by discussing a purely practical problem.

Conclusion

Shortage of cortisone and of A.C.T.H. has prompted the search for a treatment of rheumatoid arthritis which will stimulate the pituitary of the patient to secrete enough A.C.T.H. to obtain clinical improvement comparable to that achieved in the Mayo Clinic by injecting exogenous hormones. Insulin has been repeatedly tried, and, according, for example, to a recent report from the Oxford Regional Rheumatism Research Unit, with encouraging success (Kersley *et al.*, 1950). American authors, however, who gave insulin together with cortisone, had less convincing results (Henderson *et al.*, 1950), and Hench stated in a recent lecture at Edinburgh University that in the Mayo Clinic no benefit had been obtained from the combined use of insulin and cortisone. This apparent disagreement is easily explained in the light of the experiments referred to above, in which injected cortical hormones were shown to inhibit the pituitary response to stress. By giving the insulin along with the cortisone, the physician defeats his own ends, because he prevents the very release of A.C.T.H. which presumably constitutes the beneficial action of insulin in rheumatoid arthritis. Insulin can be expected to have the desired effect only if allowed to act without a simultaneous check on the action of the anterior lobe. In this instance, the fact that cortisone was probably not available to the British workers has proved to be of unexpected benefit to their patients.

REFERENCES

de Groot, J., and Harris, G. W. (1950). *J. Physiol.*, **111**, 12 P.
Gemzell, C. A. (1948). *Acta endocrinol., Kbh.*, **1**, Suppl. 1, p. 1.
Henderson, E., *et al.* (1950). *J. clin. Endocrinol.*, **10**, 800.
Hume, D. M., and Wittenstein, G. J. (1950). *Proc. First Clinical A.C.T.H. Conference*, p. 134. Blakiston Company, Philadelphia.
Ingle, D. J. (1938). *Amer. J. Physiol.*, **124**, 627.
Kersley, G. D., *et al.* (1950). *British Medical Journal*, **2**, 855.
Long, C. N. H. (1947). *Bull. N.Y. Acad. Med.*, **23**, 260.
Miller, R. A., and Riddle, O. (1942). *Amer. J. Anat.*, **71**, 311.
Sayers, G., and Sayers, M. A. (1945). *Proc. Soc. exp. Biol., N.Y.*, **60**, 162.
—— —— (1947). *Endocrinology*, **40**, 265.
—— —— Liang, T. Y., and Long, C. N. H. (1945). **Ibid., 37, 96.**
Vogt, M. (1943). *J. Physiol.*, **102**, 341.
—— (1944). Ibid., **103**, 317.
—— (1947). Ibid., **106**, 394.

OBJECTIVE ASSESSMENT OF IMPROVEMENT IN RHEUMATOID ARTHRITIS

BY

O. JANUS, M.B., B.Sc., M.R.C.P.

(From the University Rheumatism Research Centre, Manchester Royal Infirmary)

Hench (1949) has shown that most of the manifestations of rheumatoid arthritis are potentially reversible. The introduction of cortisone and A.C.T.H. has further shown that reversal can be induced by these hormones, and that many features of rheumatoid disease can be influenced within a few hours of their administration (Hench *et al.*, 1950). In prolonged and intensive courses these changes can be observed by clinical examination and by simple tests of function as shown originally by Hench and other workers in America and more recently by Copeman *et al.* (1950) in this country; and indeed Hench considers that the patient's own assessment of his degree of improvement is one of the more reliable indices of progress. Subjective improvement and simple clinical examination are, however, both very susceptible to psychological factors, and in less experienced hands these methods have led to many false claims of which those made for deoxycortone acetate and ascorbic acid by Lewin and Wassén (1949), LeVay and Loxton (1950), and others are recent examples. These difficulties have been well illustrated by the work of Quin, Mason, and Knowelden (1950).

It would clearly be advantageous to have methods of studying rheumatoid arthritis which would provide some more sensitive and measurable indices of improvement, and if these methods were delicate enough to give a reliable index of the response to single injections of cortisone or A.C.T.H. they would provide a means of comparing the responses of a variety of unknown substances with known standard active and inert preparations all in the same patient. It would also be possible to study the responses of different patients to a single standard active injection, and to compare the responses in the same patients at different stages of the disease, thus providing much valuable information.

Methods of Study

Certain features of rheumatoid arthritis seem to be suitable for detailed study.

Joint tenderness is characteristic of active rheumatoid disease, and this can be estimated clinically by squeezing a joint with the hands or fingers. It can, however, be more accurately assessed by compressing a joint between sponge-rubber cushions and recording the pressure at which pain is first experienced. The small joints of the hand, particularly the proximal interphalangeal joints so often involved in rheumatoid arthritis, are most suitable for this purpose. In the apparatus used the joints are compressed from back to front, the fingers resting on a fixed rubber cushion and being compressed by a second rubber cushion of 1.5 cm. diameter carried on a spring-loaded piston. To avoid errors due to temperature of the kind described by Kellgren, McGowan, and Hughes (1948) the hand can be kept in a water bath at 35° C. With this apparatus pain is produced in the fingers of normal subjects only when pressure exceeds 6–8 kg. In the fingers of patients with active rheumatoid arthritis pain is produced with pressures ranging from 0.25 kg. upwards, depending on the severity of the disease, and in these patients the end-point is clearly defined, readings being reproducible to within 0.25 kg. With this technique a number of joints can be tested and an average figure obtained.

Weakness of grip, often extreme, is another frequent finding in rheumatoid arthritis. This feeble grip probably results from a combination of muscular weakness, joint pain and stiffness, and flexor tendon inefficiency produced by rheumatoid tendinitis and by the painful and impacted nodules described by Kellgren and Ball (1950). As the grip could be inhibited by local pressure on painful areas a method originally suggested by Dr. H. S. Barber was evolved. A canvas-and-rubber bag was constructed of suitable size for holding in the hand, and when connected with a mercury manometer and inflated with air to a pressure of 10 mm. Hg the bag moulds itself to a deformed or stiff hand, and by asking the patient to squeeze it the power of grip can be measured by the height reached by the mercury column. The average of three grips with each hand is recorded, the figure accepted on each occasion being the highest which the subject can attain with slow steady pressure and sustain for a period of two or three seconds. Using this technique, normal subjects can always produce a pressure in excess of 300 mm. Hg, whereas patients with rheumatoid arthritis give readings usually varying between 30 and 200 mm. Hg, according to the severity of the disease, and in these patients readings are usually reproducible to within 5 mm. Hg.

Circulatory disturbances are another feature of rheumatoid disease. Local warmth is usually found over actively diseased joints, and a plethysmographic technique was therefore devised for measuring blood flows in involved knee-joints. The plethysmograph was constructed on the general lines described by Lewis and Grant (1925) and by Barcroft and Edholm (1943). The knee segment is placed in a thermostatically controlled water bath at 35° C., the knee being separated from the water by a sleeve of latex rubber held in close contact with the skin by water pressure and cuffs are placed immediately above and below the segment, the lower occluding cuff being inflated to above arterial pressure before and during readings and the upper collecting cuff being raised rapidly to venous pressure when readings are made. The patient wears standard clothing and lies supine with the head resting on one pillow. The room is maintained thermostatically at 18° C. With this technique it was found that blood flows in normal knees varied between 1 and 2 ml./100 ml./min., while in actively involved rheumatoid knees blood flows varying from 3 to 20 ml./100 ml./min. were found.

Although the joints in rheumatoid arthritis are warm the extremities, particularly the fingers, are often abnormally cool and may display Raynaud-like phenomena. Skin temperatures were therefore recorded by thermocouples on the finger-tips during the conditions of standard exposure used for the measurement of knee blood flow.

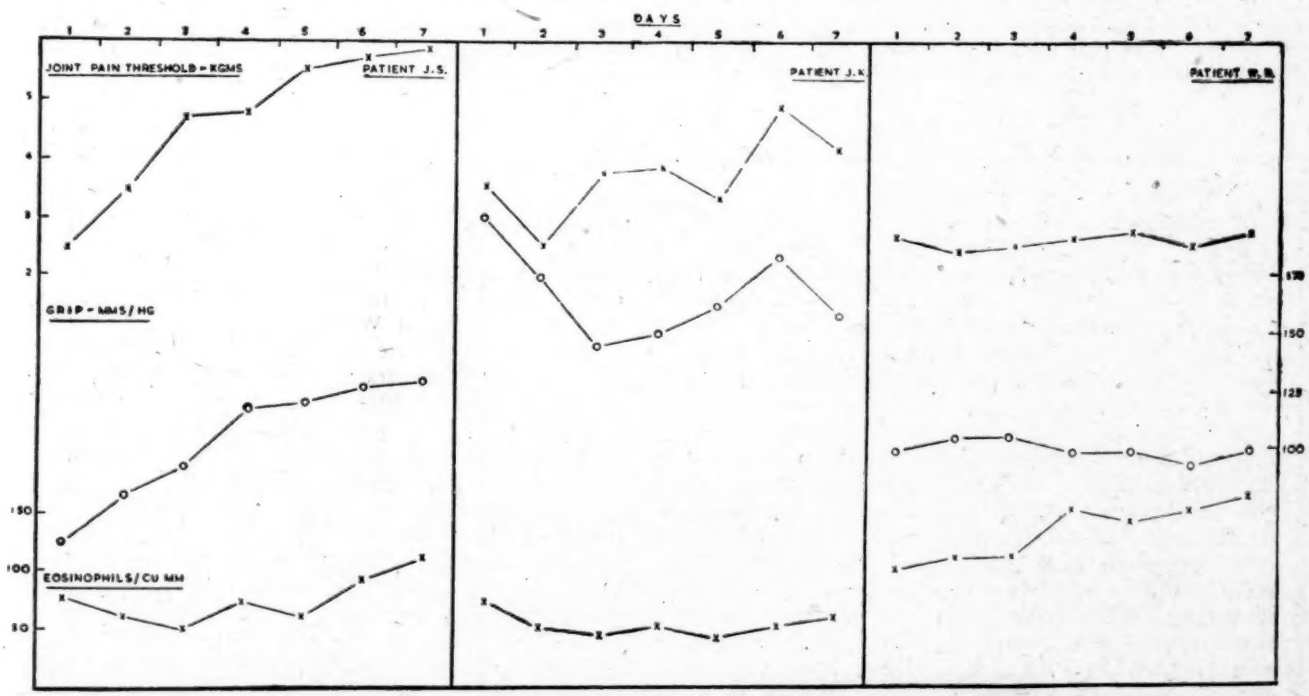


FIG. 1.—Joint-pain, grip, and eosinophil readings in three types of rheumatoid arthritis patient on a basic hospital regime of bed-rest and without treatment.

Eosinophil depression in the circulating blood following the administration of cortisone and A.C.T.H. has been widely described, and throughout these studies eosinophils were counted at appropriate intervals. The method originally described by Dunger (1910) was used and was found to be satisfactory if precautions were taken in mixing and in time of counting.

Biochemical studies were also made during the prolonged courses of A.C.T.H. and on numerous other occasions. Detailed observations were made of the E.S.R., of a modified Rose's differential agglutination test (Ball, 1950), and of urinary uric acid and creatinine excretions. Electrolyte balance studies were undertaken by Professor R. Platt, of the University Department of Medicine, and 17-kestosteroids and cortin-like substances were measured by Dr. Hain and Mr. Bassil, of the University Department of Obstetrics. The well-known changes which accompany A.C.T.H. administration were observed, but these results will not be discussed here, as they do not appear to contribute to the present discussion.

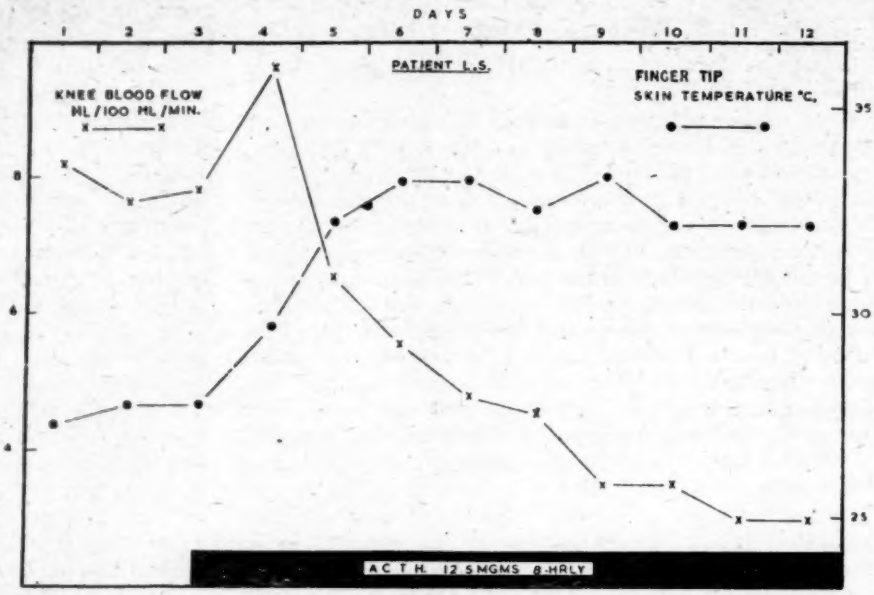


FIG. 3.—Knee blood flow and finger-tip temperature readings in a patient on 12.5 mg. of A.C.T.H. 8-hourly for 10 days.

Selection of Patients

These methods of study were applied to hospital in-patients suffering from rheumatoid arthritis in whom disability was judged to be mainly due to active reversible disease. The patients studied all had multiple joint involvement with radiological signs at least of osteoporosis; other stigmata of rheumatoid disease, such as constitutional disturbance, raised sedimentation rate, nodules, tendon lesions, and lymphadenopathy, were also present. These patients were placed on a basic hospital regime of rest in bed, during which drugs were not given. Daily or twice-daily measurements were made, and the results compared with daily standard clinical assessments of functional capacity and of joint pain, swelling, and range of movement. Three types of patient were identified, and an example of each type is recorded in Fig. 1.

Patient J. S. showed a steady improvement in all readings from day to day, and her subsequent progress and clinical assessment confirmed that she was going into spontaneous remission on rest in bed. Patient J. K. showed marked fluctuations in all readings from day to day, and these fluctuations were more pronounced than those revealed by standard clinical assessment. Patient W. B showed only small fluctuations from day to day, and at the end of a week there had been little change in her measurements, and no change had been recorded in her general clinical assessment.

Patients of this last type, with active disease as defined above, were considered to be relatively stable but potentially reversible cases of rheumatoid arthritis and were selected for special study.

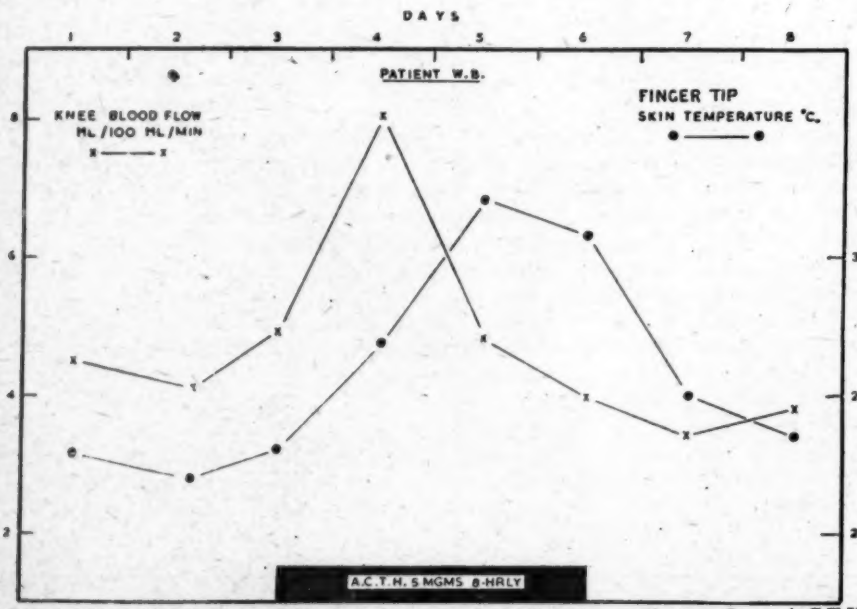


FIG. 2.—Knee blood flow and finger-tip temperature readings in a patient on 5 mg. A.C.T.H. 8-hourly for 72 hours.

Results of Studies

Having selected patients of the type described it was necessary to determine if the methods used were sensitive enough to demonstrate the effects of a single dose of an active hormone. To eliminate psychological factors patients were told that they would receive a series of injections, most of which would be inactive, and in fact injections of normal saline or other inert substances were given at frequent intervals, and studied with equal intensity. The detailed effects were observed of single injections of 25 mg. of A.C.T.H. in six patients, of 5 mg. of A.C.T.H. given eight-hourly for 72 hours in four patients, of 12.5 mg. of A.C.T.H. given eight-hourly for 10 days to two patients, and of 200 mg. of cortisone acetate given in a single injection to five patients.

After a single injection of 25 mg. of A.C.T.H. (see Fig. 4) improve-

ments occur in joint tenderness and grip, rising to a maximum in between six and eight hours, then falling, often to a rebound level within 24 hours, and returning to around the original level within 48 hours. During this period the circulating eosinophils are depressed, the maximum depression occurring between four and six hours after injection, preceding by about two hours the changes in joint tenderness and grip. The knee blood flow shows a diphasic response, a variable initial increase at six hours being followed by a rapid decrease between 8 and 12 hours. The skin temperature shows no change. If 5 mg. of A.C.T.H. is given eight-hourly for 72 hours the joint tenderness and grip improve more slowly, rising to a maximum at the end of this period, and the eosinophils become moderately depressed and remain so throughout the period. The knee blood flow, after showing an initial increase at the end of six hours, decreases to a lower level by the end of the period, and this decrease is accompanied by a rise in skin temperature on the finger-tip (Fig. 2). When 12.5 mg. of A.C.T.H. is given eight-hourly for 10 days these changes become very large. There is complete remission in joint tenderness up to normal levels, the grip becomes much improved, and the eosinophils remain greatly depressed throughout the course. Knee blood flow decreases steadily over the period following an initial increase, and finger-tip skin temperature rises and remains high (Fig. 3). After stopping these repeated injections the changes observed do not return to their original level in 48 hours but may remain at a new level for days or weeks.

With a single injection of 200 mg. of cortisone acetate (see Fig. 4) a slower series of responses occur, presumably due to slowness of absorption. Joint tenderness and grip show no tendency to improve for at least eight hours, and then rise slowly to a maximum in between 24 and 48 hours. The eosinophil depression is maximal at about 24 hours. Knee blood flows have not shown the initial increase found with A.C.T.H., but decrease to a lower level in between 24 and 48 hours. One of the five patients tested with cortisone gave no response and was afterwards shown to be also refractory to A.C.T.H. During this series of observations no significant deviations in the curves were produced by injections of normal saline and other inert substances.

From this series of observations it was clear that with all these active agents grip and joint tenderness improved rapidly and eosinophil counts fell. The circulatory changes were interesting but more complex, the initial change in knee blood flow being either an increase or a decrease with single injections, and with repeated injection an eventual decrease in joint blood flow associated with a rise in finger-tip skin temperature. It was felt that this variable initial response precluded the use of joint blood-flow measurements as indicators of responses to single injections and that further studies would be needed to demonstrate their significance.

With the use of these techniques it was decided to make a preliminary survey of some substances claimed to be effective in rheumatoid arthritis, and simultaneously to determine if consistently positive results were obtained with substances of known potency. Suitable patients were selected by the methods already described, and they were told that they would be receiving a series of injections or tablets, most of which would be ineffective; but all patients received at least one injection of A.C.T.H. to demonstrate that they were in fact capable of responding, and at least one injection of normal saline to demonstrate any psychological response. In many instances also the observer did not know what substance had been given. An example of one experiment is shown in Fig. 4, in which the effects of 4.8 mg. of an A.C.T.H. peptide from the chemical and

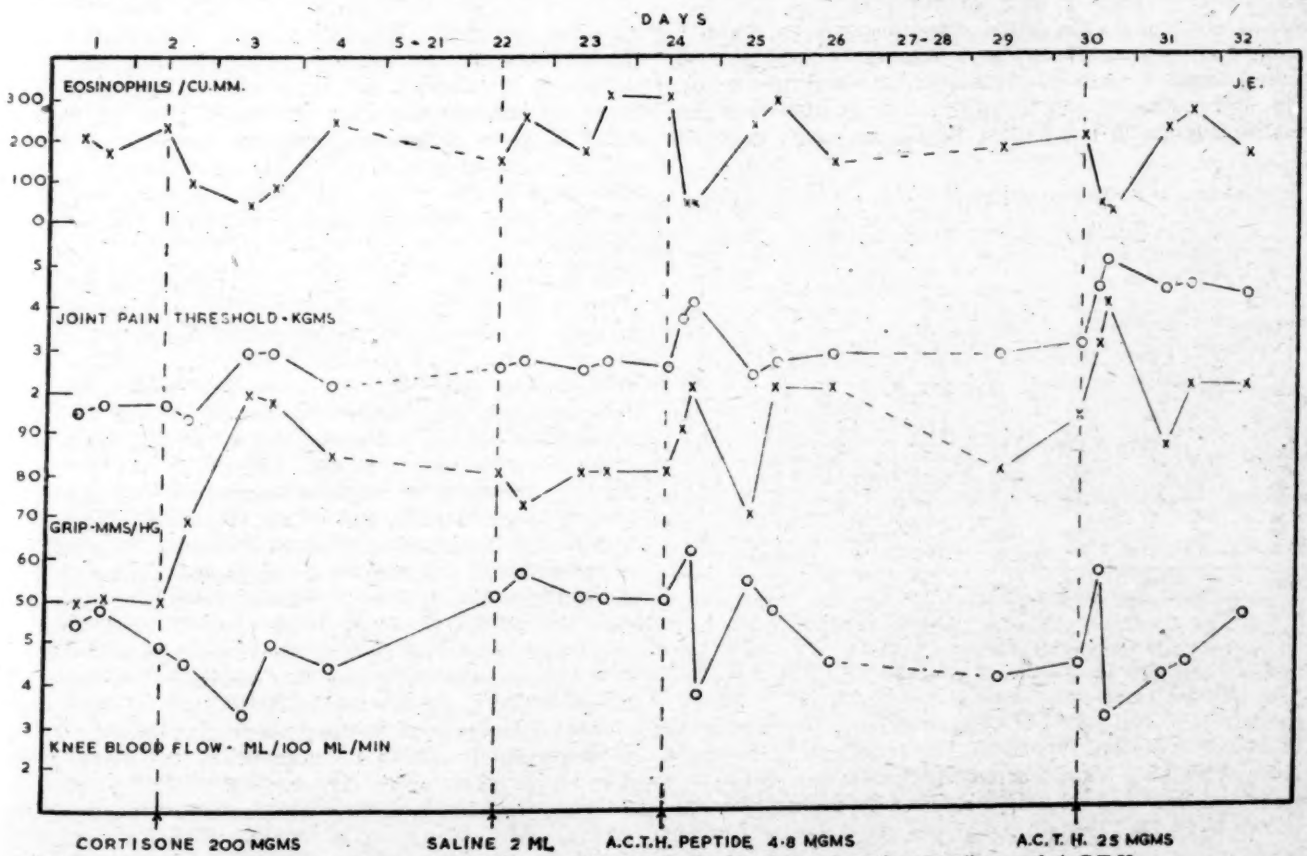


FIG. 4.—Effects of 4.8 mg. of A.C.T.H. peptide compared with those of cortisone, saline, and A.C.T.H.

biochemical laboratories at Cambridge University were compared with 25 mg. of the original A.C.T.H. from which it had been prepared, with 200 mg. of cortisone acetate, and with normal saline. The magnitude and type of response to this A.C.T.H. and its peptide are very similar, and in this case biological assays in the Cambridge Laboratories had suggested that 4.8 mg. of this peptide fraction should be equivalent to 25 mg. of the original A.C.T.H., which had a potency 1.93 times that of the Armour standard L.A.1A.

In suitable patients studies of this kind continued over prolonged periods showed that without special therapy small fluctuations occurred in grip, in joint tenderness, and in circulating eosinophils, but these random fluctuations were small and often in opposite senses, improvement in grip being accompanied by deterioration in joint tenderness while the eosinophils fluctuated independently. With cortisone and A.C.T.H. fluctuations were always larger and in the same sense, a fall in eosinophils being accompanied by improvement in both grip and joint tenderness. It is clearly desirable to summate these fluctuations after giving them each a comparable weighting. As a standard the response six hours after a single injection of 25 mg. of A.C.T.H. has been taken. In 10 patients to whom the dose was given the average increase in grip was 26 mm. Hg, the average increase in pressure required to produce joint pain was 1 kg., and the average fall in eosinophils was 77% of the original count (see Table). Defining each of these as a unit of fluctuation, the scatter diagrams in Figs. 5 and 6 have been constructed. Fig. 5 represents the result of adding together units of fluctuation in joint tenderness, grip, and eosinophil counts, and each point represents this total fluctuation in one patient during the period stated in the left-hand column. The whole diagram represents the results of trials on 18 patients, each patient having been given at least one known active injection, one control injection, and one or two trial injections on the general plan shown in Fig. 4. Certain substances could not be expected to cause eosinophil fluctuations, and Fig. 6 has been similarly constructed, each point representing the summation of fluctuations in joint tenderness and grip only. Since the average deviation six hours after 25 mg. of A.C.T.H. is by definition 3 units in the case of Fig. 5 and 2 units in the case of Fig. 6, interrupted lines have been drawn in at half these values to represent the mid-point between absent response and average response.

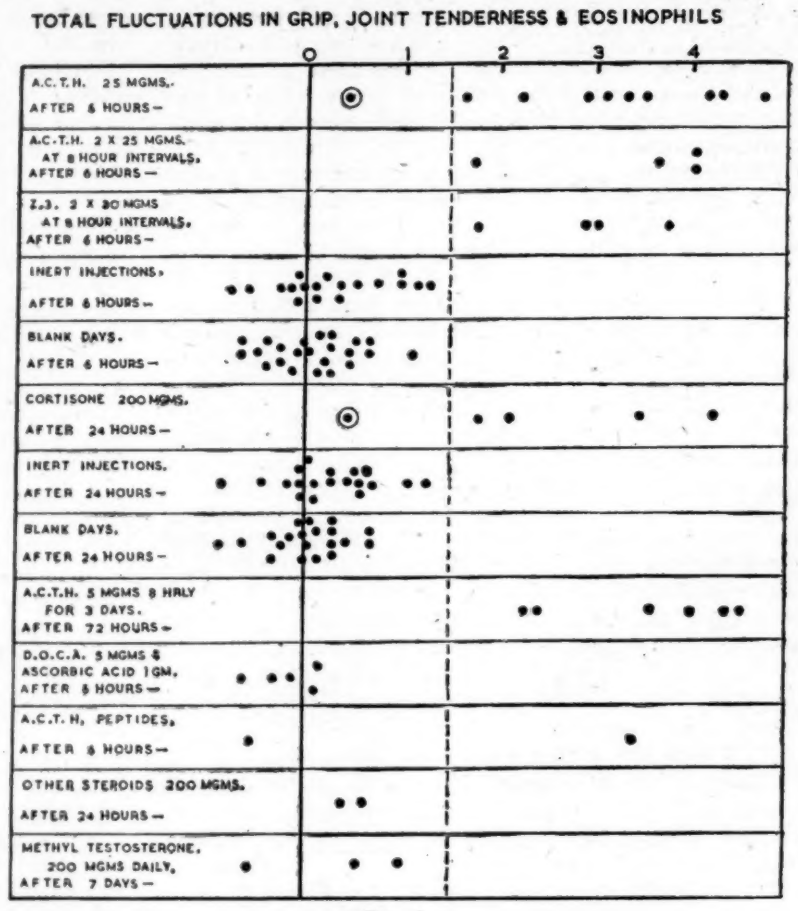

TOTAL FLUCTUATIONS IN GRIP, JOINT TENDERNESS & EOSINOPHILS
0
1
2
3
4
A.C.T.H. 25 MGMS. AFTER 6 HOURS —
A.C.T.H. 2 X 25 MGMS. AT 8 HOUR INTERVALS, AFTER 6 HOURS —
Z.3. 2 X 20 MGMS AT 8 HOUR INTERVALS, AFTER 6 HOURS —
INERT INJECTIONS, AFTER 6 HOURS —
BLANK DAYS. AFTER 6 HOURS —
CORTISONE 200 MGMS. AFTER 24 HOURS —
INERT INJECTIONS. AFTER 24 HOURS —
BLANK DAYS. AFTER 24 HOURS —
A.C.T.H. 5 MGMS 8 HRLY FOR 3 DAYS. AFTER 72 HOURS —
D.O.C.A. 5 MGMS & ASCORBIC ACID 1GM. AFTER 6 HOURS —
A.C.T.H. PEPTIDES, AFTER 6 HOURS —
OTHER STEROIDS 200 MGMS. AFTER 24 HOURS —
METHYL TESTOSTERONE, 200 MGMS DAILY, AFTER 7 DAYS —

FIG. 5.

Fluctuations in 10 Patients Measured 6 Hours After 25 mg. of A.C.T.H.

Patient	Eosinophil % Change	Pain Threshold Change (kg.)	Grip Change (mm. Hg)	Eosinophil Unit Change	Pain Threshold Unit Change	Grip Unit Change	Total Fluctuations
H.J. ..	−100	+0·9	+25	+1·3	+0·9	+1·0	+3·2
A.J. ..	−74	+0·7	+25	+1·0	+0·7	+1·0	+2·7
J.E. ..	−90	+2·1	+25	+1·2	+2·1	+1·0	+4·3
R.K. ..	−72	+1·9	+52	+0·9	+1·9	+2·0	+4·8
E.M. ..	−98	+1·5	+40	+1·3	+1·5	+1·5	+4·3
D.S. ..	−90	+0·9	+10	+1·2	+0·9	+0·4	+2·5
R.S. ..	−82	+0·8	+25	+1·1	+0·8	+1·0	+2·9
M.W. ..	−25	—	+2	+0·3	—	+0·1	+0·4
K.M. ..	−86	+0·6	+45	+1·1	+0·6	+1·7	+3·4
W.B. ..	−52	+0·4	+15	+0·7	+0·4	+0·6	+1·7
Total ..	−769	+9·8	+264				
Average fluctuations = 1 unit ..	−76·9	+0·98	+26·4				

In commenting on these results, it is clear that A.C.T.H given in any of the three doses tested and cortisone given in single injections produce deviations which are outside the limits of chance deviations occurring on blank days or deviations associated with inert injections. The only exceptions are the ringed observations, all four of which occurred in the one refractory patient already mentioned. Apart from the active peptide (also illustrated in Fig. 4) the only substance so far used which produced significant deviations was aspirin, and of the 10 patients tested three appeared to be sensitive and seven insensitive. It is perhaps of interest that this sensitive group showed an eosinophilia in response to aspirin—a phenomenon we have also observed in four cases of acute articular rheumatism of rheumatic fever type. The group labelled steroids includes two compounds supplied by the Chemistry Department of this University, Δ5-cholene-3β 25-diol and 17α-allyl testosterone. The peptide fraction which gave no response was subsequently found to be inactive by rat assay at the Cambridge laboratories. The column labelled A.C.T.H.-Z3 contains results of preliminary trials with a new preparation of A.C.T.H.

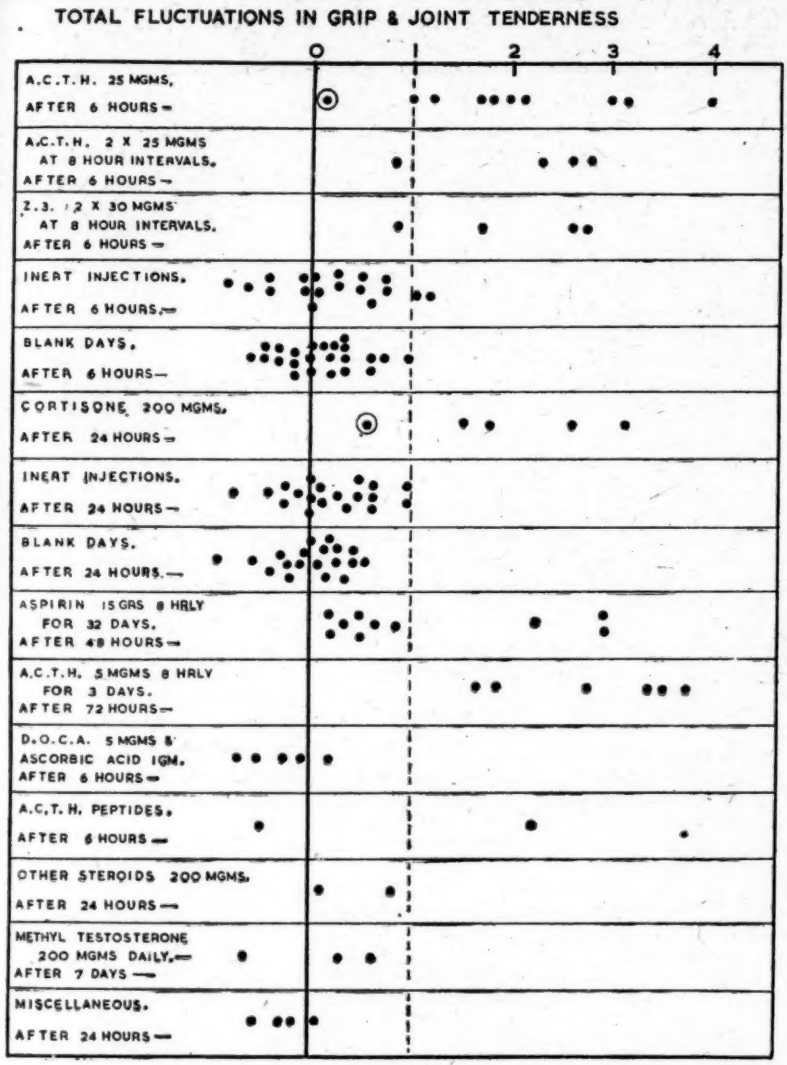

TOTAL FLUCTUATIONS IN GRIP & JOINT TENDERNESS
0
1
2
3
4
A.C.T.H. 25 MGMS. AFTER 6 HOURS
A.C.T.H. 2 X 25 MGMS AT 8 HOUR INTERVALS. AFTER 6 HOURS
Z.3. 2 X 30 MGMS AT 8 HOUR INTERVALS. AFTER 6 HOURS
INERT INJECTIONS. AFTER 6 HOURS
BLANK DAYS. AFTER 6 HOURS
CORTISONE 200 MGMS. AFTER 24 HOURS
INERT INJECTIONS. AFTER 24 HOURS
BLANK DAYS. AFTER 24 HOURS.
ASPIRIN 15 GRS 8 HRLY FOR 32 DAYS. AFTER 48 HOURS
A.C.T.H. 5 MGMS 8 HRLY FOR 3 DAYS. AFTER 72 HOURS
D.O.C.A. 5 MGMS & ASCORBIC ACID 1GM. AFTER 6 HOURS
A.C.T.H. PEPTIDES. AFTER 6 HOURS
OTHER STEROIDS 200 MGMS. AFTER 24 HOURS
METHYL TESTOSTERONE 200 MGMS DAILY. AFTER 7 DAYS
MISCELLANEOUS. AFTER 24 HOURS

FIG. 6.

The spread in deviation from 1.5 to 4.5 units among the active substances is largely due to variations in individual sensitivity, and underlines the necessity for establishing the degree of sensitivity and for comparing drugs in the same patient at times not far separated.

Discussion

From the data presented it is clear that the response of rheumatoid patients to substances with cortisone-like or A.C.T.H.-like activity can be measured with some accuracy. Small single injections allow the patient to return to his original level in 48 hours, but repeated injections often cause prolonged changes in the patient's condition after they have been discontinued. Thus, provided that only single injections are given, the responses in a single patient may be used to compare the potencies of different preparations of these hormones, and unknown substances may be rapidly evaluated by comparison with A.C.T.H. or cortisone of known potency. Apart from such practical considerations, a study of these responses in different patients and at different stages in the disease process may produce some further information about the role of adrenocortical activity in rheumatic diseases.

The mechanism of the interesting changes induced by cortisone and A.C.T.H. in joint blood flow and in finger-tip skin temperature also requires further investigation both in the normal and in patients with the more severe Raynaud-like syndromes which are found in a variety of rheumatic and peripheral vascular diseases.

Summary

Sensitive and reliable methods for studying some of the features of rheumatoid arthritis have been evolved. These include measurements of joint tenderness and the power of grip as well as plethysmographic studies of knee blood flow.

In suitable patients these methods can be used to study in detail the response to single injections of cortisone or A.C.T.H., and the responses to these substances have been compared with those obtained from inert control injections, and with other substances of unknown potency.

In rheumatoid arthritis knee blood flow is raised while the finger-tips remain abnormally cold. Administration of A.C.T.H. and cortisone reverses these changes, the knee blood flow falling towards normal while the finger-tip temperature rises.

When more cortisone and A.C.T.H. become available much useful information may be gained by studying the responses to standard doses in different patients, and in the same patient at different stages in the disease process.

Much of the A.C.T.H. used in these studies was donated through the kindness of Dr. W. Tindall, of Messrs. Organon Ltd. Cortisone and other A.C.T.H. were supplied through the courtesy of the Medical Research Council. The A.C.T.H. peptides were provided through Professor A. R. Todd, F.R.S., and Professor F. G. Young, F.R.S., of Cambridge University. The $\triangle$5-Cholene-3β 25-diol and 17α-allyl testosterone were supplied through Professor R. E. Jones, of the University of Manchester. Thanks are due to Dr. R. Moore, who made many of the routine clinical assessments, and particularly to Dr. J. H. Kellgren for advice and criticism throughout.

REFERENCES

Ball, J. (1950). *Lancet*, **2**, 520.
Barcroft, H., and Edholm, O. G. (1943). *J. Physiol.*, **102**, 5.
Copeman, W. S. C., Savage, O., Bishop, P. M. F., Dodds, E. C., Gottlieb, B., Glynn, J. H. H., Henly, A. A., and Kellie, A. E. (1950). *British Medical Journal*, **2**, 849.
Dunger, R. (1910). *Münch. med. Wschr.*, **57**, 1942.
Hench, P. S. (1949). *Ann. rheum. Dis.*, **8**, 90.
—— Kendall, E. C., Slocumb, C. H., and Polley, H. F. (1950). *Arch. intern. Med.*, **85**, 545.
Kellgren, J. H., and Ball, J. (1950). *Ann. rheum. Dis.*, **9**, 48.
—— McGowan, Anna J., and Hughes, E. S. R. (1948). *Clin. Sci.*, **7**, 13.
LeVay, D., and Loxton, G. E. (1950). *Lancet*, **1**, 209.
Lewin, E., and Wassén, E. (1949). Ibid., **2**, 993.
Lewis, T., and Grant, R. T. (1925). *Heart*, **12**, 73.
Quin, C. E., Mason, R. M., and Knowelden, J. (1950). *British Medical Journal*, **2**, 810.

A two years' antimalarial campaign began in British Honduras in May, with the help of a grant of $22,000 from the United Nations Children's Emergency Fund (U.N.C.E.F.). Malaria is endemic and a principal cause of sickness, being responsible for up to 20% of hospital admissions and 9% of certified deaths in the colony; and it is hoped that by spraying every single house twice a year with 5% emulsion of D.D.T. in xylol, and by distributing free prophylactic "paludrine" to selected schools as well as using the well-known routine measures, the great success achieved in similar campaigns in Cyprus and British Guiana will be repeated here.

ALOPECIA AREATA: A CLINICAL STUDY

BY

IAN ANDERSON, M.B., B.Sc., M.R.C.P.

Senior Registrar, Rupert Hallam Department of Dermatology, Royal Infirmary, Sheffield

Alopecia areata is a disease quite commonly encountered in hospital practice. It was present in 2% of the 15,000 new patients seen at this clinic in 1937–41.

This paper is based on a clinical study of 114 almost consecutive unselected cases seen in hospital during the past two years. The series was made up of 81 cases of simple alopecia areata of the type which recovers after a few months, 24 cases of alopecia totalis and universalis (the initial lesions being those of alopecia areata and therefore considered to be the extreme degrees of this condition), and 9 cases of persistent alopecia areata which had been present for a period of years.

Age, Sex, and Colour of Hair

There were approximately an equal number of male and female subjects (59 male, 55 female) and for the most part the disease seems to affect both sexes equally. Brown (1929) found that with increasing age females predominated over males, but in this series there were equal numbers even over the age of 30.

These patients do not represent a true cross-section of the cases of alopecia, as many are treated in a children's hospital in the area. However, the age at which the disease first occurred was recorded; this showed that 50 (44%) were attacked before the age of 21. There were, however, 22 (19.5%) over the age of 40 (Table I). Brown, in a series of 300 cases, found a considerably higher proportion of children (57% under 21) and only 9% over the age of 40

TABLE I.—*Age at Onset and Prognosis*

Age at Onset of First Attack	No. of Cases	% Cases in which Disease Persisted or Extended to Complete Baldness
0–10 years	23	45
11–20 ,, ...	27	33
21–30 ,, ...	23	19
31–40 ,, ...	19	
Over 40	22	23
	114	

The hair colour was recorded in 82 cases; 37 (45%) were dark haired compared with 42 (51%) in a control series of out-patients (Table II).

TABLE II.—*Hair Colour*

	Alopecia Cases	Out-patients
Fair	16	20
Medium	29	20
Dark	37	42
Total	82	82

Cockayne (1933) stated that the disease is much commoner in dark-haired subjects; in this series, at least, the difference appears to be due to the higher proportion of dark hair in the population of this city.

The Disease

The best descriptions of alopecia areata are probably those of Sabouraud (1936). The pattern that he described was shown well in most of the cases. The disease begins as one patch, and this may remain single or, after a few weeks, secondary patches may appear on other parts of the scalp. Charting of the position of this first patch revealed a significant difference between the sexes (Table III). Of the males, 35 had occipital patches and 15 fronto-vertical, while the females showed a reversed distribution—15 occipital and 31 fronto-vertical. This has not been previously recorded, to my knowledge, and may indeed be a distortion due to hospital selection (occipital patches in females passing unnoticed). Five male cases had the first patch on the beard area, and the primary patch may presumably occur on any hairy part of the body.

TABLE III.—*Position of Primary Patch*

Position	Present Series		Kinnear and Rogers Series of Scalp Ringworm; % Incidence	
	Male	Female	Male	Female
Occiput	35 (60%)	15 (27%)	56	32
Vertex	8 } (25%)	15 } (56%)	6	22
Frontal	7 }	16 }		
Parietal	4 (7%)	9 (16%)	9	17
Beard	5	—		
	59	55		

Before dismissing the primary patch it is interesting to compare the figures with those of Kinnear and Rogers (1948) for the position of ringworm of the scalp in 505 boys and 93 girls. The higher incidence of occipital primary infection in boys compared with girls (56% to 32%) was taken as evidence of barber-shop infection. Their figures are strikingly similar to the present series (Table III).

The secondary patches may appear anywhere on the scalp, beard, eyebrows, or body hair. The loss of one eyebrow has not the same bad prognosis as the fall of both eyebrows and lashes in the universalis cases.

Of the 114 cases 81 were those with single or multiple patches which run their course in four to twelve months.

The 24 cases of alopecia totalis and universalis are in no way an indication of the incidence of this condition; they were seen because the patients attended for a Health Service wig. Most of them had been bald for many years and the condition was regarded as permanent. All cases began in the same way as ordinary alopecia areata, but after the appearance of the secondary patches a general fall of the hair occurred, starting with eyebrows and lashes and followed by pubic, axillary, and body hair in most cases. It is interesting to note that areas not actually attacked at this time may grow hair in later life; one female patient without a hair on any of the usual areas had a marked post-menopausal facial hirsutism.

Only one case was followed from the primary patch through all the stages to complete and probably permanent universal baldness. Four cases were followed from their onset through to the totalis stage, but later on hair grew satisfactorily. An interesting point in many of the histories is that in recovery from a severe attack the primary patch is often the last to be covered. It is as if the first area is attacked more severely than the others and the follicles are more permanently affected.

The third type of case is that which may be called persistent alopecia areata. There are nine of these, and it is possible to divide them into: (1) small recurrent patches which heal and reappear continuously over a period of years, and (2) the slowly advancing type, which may be band-like (ophiasis) or round in shape and fronto-vertical in position. This appears to differ little from the ordinary alopecia except in its prognosis. Four of the second type

which have been observed for the past 18 months show little sign of change except for some alteration in the shape of the patches.

Recurrence Rate.—A previous attack of the disease had occurred in 32 cases (28%). Walker and Rothman (1950), in a follow-up of 120 cases for 5 to 20 years, reported an overall relapse rate of 86%, and believe that all cases will be found to relapse if followed long enough.

Family History

In 22 cases (19%) alopecia areata occurred in another member of the family. At first sight this would appear conclusive of a familial tendency; it agrees well with Brown (1929) and Sabouraud (1929), both of whom found a 20% family incidence. However, we could discover no account of the incidence of alopecia in the population as a whole, and in view of this 320 traumatic orthopaedic out-patients were interviewed. Eight had a history of alopecia areata, and it is possible that this incidence of 2.5% may be a little on the low side. One of the parents of the 22 familial cases had been affected in seven and a brother or sister in eight. It would be interesting to compare these figures with the families of normal subjects, as the incidence suggests there may be little difference. In Brown's 135 cases, a parent was affected in only 8 of the 28 familial cases. There was only one case in the present series with a multiple family history (grandparent and father).

It must also be noted that in 7 out of these 22 cases alopecia areata occurred in near relatives at the same time as in the patient. In none of these seven was there an obvious cause which may have affected the whole family. Savill (1944) mentions multiple cases in the family and finds it difficult to explain. It may be said that two other patients had intimate friends who suffered at the same time as themselves.

Precipitating Cause of Attack

The commonest precipitating cause was found to be mental shock or acute anxiety. If alopecia followed a few weeks after such an event then that was taken to be the cause. In 27 cases (23%) the alopecia had been preceded by some form of mental stress. In a control series interviewed by members of the Scientific Advisory Committee of the Empire Rheumatism Council (1950) 9% of 292 subjects reported some form of mental trauma within three months previous to the investigation. A further 26 cases were obviously suffering from various degrees and forms of mental disturbance, or what the patients themselves called "nerves." They had, however, been in this state for years, and it was not related chronologically in any way to the appearance of the alopecia.

It is concluded that the incidence of precipitating shock (23%) is too large to be due to chance. It is interesting to note that the incidence of mental disorder is no higher in cases of severe alopecia than in the series as a whole (Table IV).

TABLE IV

	Whole Series	Cases of Persistent or Total Alopecia
Total number	114	33
No. with carious teeth	17	4
" " clinically infected throats	18	4
" " precipitating shock or worry	27	8
" " emotional instability not related to attack	26	7

In addition to these 53 cases of possibly nervous origin other cases included: (1) Three cases of general infection—one of influenza and two of measles. (2) One case of local infection: this followed a boil on the scalp, and was true alopecia areata and not the usual type of post-infective alopecia. (3) One case of local trauma: alopecia appeared on the area of trauma to the scalp. (4) One case of pregnancy: patches recurred at each pregnancy. (5) Four cases in which the patient felt unwell before the onset, nothing was found physically, and the cause was not apparently mental in origin.

It may be as well here to mention focal sepsis: 15% showed some degree of carious teeth, a figure which does not suggest that it is a frequent cause of the condition, and 16% had clinically infected throats. The incidence of these conditions is no higher in the severe alopecia cases than in the whole series (Table IV), and I cannot believe that they play a big part in the aetiology.

Thirty-one cases (27%) were found both physically and mentally to be in perfect health.

Prognosis

The prognosis of a case of alopecia areata seen in the early stages is difficult to judge. It seems that most cases recover, but to give a definite opinion is impossible. Later in the course of the disease a generalized fall of hair with complete loss of eyebrows and whitening or loss of eyelashes is grave, and when this generalized loss is rapid the case very rarely recovers. Cases of alopecia totalis without loss of body hair may recover even after a year or more, but alopecia universalis appears to be nearly always permanent. Even if there is some recovery it is rarely lasting and the condition relapses. Two factors in the history have been said to have an adverse effect on the outlook. A positive family history is the first of these. Yet in this series there were 19% with such a history in the 33 severe and persistent cases, compared with 20% for the 81 simple cases. Even if we accept the familial tendency it does not seem to influence the prognosis. Age of onset is another factor mentioned by some, and it will be seen from Table I that the disease appears to have the graver prognosis in children. Walker and Rothman (1950) also found that the prognosis was less favourable for children than adults (50% went on to total baldness, compared with 23% in adults). Of the 32 cases with a previous history of alopecia 6 became generalized, and of the 82 with no previous history 18 took a similar course.

From wigs provided it is estimated very roughly that the incidence of complete baldness in this district must be at least 1 in 5,000, and, presuming a disease incidence of 2–3%, we arrive at the possibility that 1 in 150 patients with alopecia areata can look forward to a permanent disability. The figures given in Table I are purely comparative and are probably far in excess of the true prognosis. Walker and Rothman (1950), however, believe that even in adults 23% of the cases proceed to total baldness, and that 75% of these remain permanently bald. I can account for these high figures only by presuming that they were dealing exclusively with very severe cases from the start.

Of persistent alopecia areata I can say little. I feel that patients with small recurrent patches usually eventually recover, while some of the ophiasis type progress to permanent complete baldness.

Associated Conditions

Five out of the 114 cases had associated vitiligo. The presence of that condition among the population is uncommon, and this incidence of 4% may, I feel, be significant. Roxburgh (1929) found no association with vitiligo

in his series of cases. Nail changes seen in alopecia are interesting and quite common: 13 out of the 24 totalis and universalis cases showed them, and three other cases with simple patches had them in a minor degree. Leuconychia was not included, as this is not uncommon in normal subjects.

Nail changes fall into two groups: (1) longitudinal striations with a serrated nail edge, and (2) the pitted nail not unlike that of psoriasis. Sabouraud (1936) described these changes and said that when they are present the prognosis is hopeless.

Discussion

The aetiology of alopecia areata has been and still is the centre of considerable speculation. Early writers attempted to find one cause for all cases, which, as seen in this series, is a difficult task. There seem to be two likely causes.

The first, and probable, explanation is that the alopecia represents the reaction of the body to stress—i.e., it is, in modern terminology, a disease of adaptation. Barber (1950), in a discussion of psoriasis, included alopecia areata in the same group as psoriasis and thought that they were examples of diseases of adaptation. Stresses which may result in alopecia in a person with the hair as a "target area" are trauma, mental stress, and infection.

The other explanation, a possibility which we must still consider, is that of a virus infection. Since Sabouraud, opinions have been much against infection, but alopecia would agree well with a virus disease. We might visualize a virus which, like herpes simplex, remains dormant in the scalp and which with stress multiplies to cause the primary patch, this being followed in some cases by a general infection and an attack on all hairy parts and the nails. Attempts to infect subjects with alopecia have always failed, but I doubt if this can be taken as conclusive evidence. Epidemics of so-called alopecia areata have also been largely discounted in recent years.

For the present we must content ourselves with the knowledge of the precipitating causes only.

Summary

Alopecia areata was found in 2% of the 15,000 skin outpatients seen in a five-year period, and 2.5% of 320 orthopaedic patients had a past history of the condition.

The present series of 114 cases consists of 81 of simple alopecia areata, 24 extensive cases, and 9 of persistent areata.

The incidence seems to be the same in both sexes, and was not related to the colour of the hair. The disease occurs at all ages but is commonest in the younger age group.

There appears to be a difference in the position of the primary patch between the sexes—male: 60% occipital, 25% fronto-vertical; and female: 27% occipital, 56% fronto-vertical. A previous history of the disease was found in 28%.

A positive family history was present in 19%, but it is doubted if this is really significant of a familial tendency. Other members of the family were affected at the same time in 6% of cases.

Mental trauma was a precipitating cause in 23%. Focal sepsis is thought to play little part in the causation and was no more prominent in extensive cases than in those which recovered. In 27% the health, both physically and mentally, was excellent.

Vitiligo was present in 4% of cases. Nail changes are common in extensive alopecia.

The prognosis is difficult to give in an individual case, but probably less than 1% suffer permanent ill effects. The prognosis is graver when the disease occurs before 10 years of age, but is little affected by other factors in the history.

The aetiology is unknown; alopecia could be either a disease of adaptation or possibly a virus disease.

I wish to thank Dr. H. R. Vickers, Dr. I. B. Sneddon, and Dr. Doris Fletcher for permission to publish this series.

REFERENCES

Barber, H. W. (1950). *British Medical Journal*, **1**, 219.
Brown, W. H. (1929). *Brit. J. Derm. Syph.*, **41**, 299.
Cockayne, E. A. (1933). *Inherited Abnormalities of the Skin*. Oxford Univ. Press, London.
Kinnear, J., and Rogers, J. (1948). *British Medical Journal*, **2**, 854.
Report by Scientific Advisory Committee of Empire Rheumatism Council (1950). Ibid., **1**, 799.
Roxburgh, A. C. (1929). *Brit. J. Derm. Syph.*, **41**, 351.
Sabouraud, R. (1929). *Maladies du Cuir Chevelu, Les Syndromes Alopéciques*. Masson, Paris. Quoted by Cockayne (1933).
—— (1936). In J. Darier, *et al.*, *Nouvelle Pratique Dermatologique*, vol. 7, chapter 6. Masson, Paris.
Savill, Agnes (1944). *The Hair and Scalp*. Arnold, London.
Walker, S. A., and Rothman, S. (1950). *J. invest. Derm.*, **14**, 403.

TREATMENT OF THYROTOXICOSIS WITH 2-MERCAPTOIMIDAZOLE

CLINICAL IMPRESSIONS

BY

GEORGE L. FOSS, M.A., M.D.

Clinical Assistant, Department of Medicine and Gynaecological Out-patient Department, Bristol Royal Hospital

The use of antithyroid drugs of the thiouracil series is undoubtedly established; however, as with all other treatments of thyrotoxicosis, relapse occurs in some cases and there is also the possibility of toxic effects. In many cases relapse is due to an aversion to continuing adequate treatment with a potentially toxic substance or to accepting its permanent use in maintenance doses in the same way as with thyroid substitution therapy in myxoedema. Thyrotoxic subjects treated with antithyroid drugs should be under supervision at regular intervals by units organized for long-term follow-up, with all the necessary facilities and attention, as with diabetes. In this way the patients would benefit from better control, and an opportunity would be provided for careful and concentrated study of thyroid disease.

With the use of some of the more recently introduced antithyroid drugs the toxicity factor has been much reduced, but not eliminated, and Stanley and Astwood (1948), by employing radioactive iodine tests, have been able to compare the potency of these newer drugs in man. They claim that 2-mercaptoimidazole is approximately five times more potent than methyl thiouracil; and Astwood (1949—personal communication) reports that methyl mercaptoimidazole is about 10 times more potent than 2-mercaptoimidazole.

Stanley and Astwood (1948) have briefly reported the efficacy of treatment with 2-mercaptoimidazole in a series of 20 patients with thyrotoxicosis; they found that 40–100 mg. daily was an adequate therapeutic dose. Even in severely thyrotoxic subjects a dose of 20 mg. sometimes produced nearly complete inhibition of hormone synthesis lasting as long as 11 hours. In others a dose of 20 mg. was only partially effective.

In May, 1949, 2-mercaptoimidazole became available for clinical trial in this country, and this paper reports the results of treatment of a small series of cases.

Toxicity of 2-Mercaptoimidazole in Animals

The acute toxicity of the antithyroid substances varies according to the experimental animals used, the strains selected, the diet, and other factors. Comparative data obtained in this way will not necessarily give the ratio for man. Astwood (1943a) stated that the minimal lethal dose (M.L.D.) of 2-thiouracil in rats was more than 100 times the dose required to produce a detectable thyroid effect Toxic manifestations in rats were not seen with 2-thiouracil until a daily dose of 100 mg. per 100 g. body weight was exceeded (Astwood, 1943b). Although direct comparisons are unsatisfactory, owing to variations in techniques, it would seem that 2-mercaptoimidazole has an acute toxicity similar to that of thiouracil and that methyl mercaptoimidazole is about seven times more toxic, although much more active. If this is accepted, a comparative therapeutic index may be expressed as follows:

Thiouracil	$\frac{\text{Activity}}{\text{Toxicity}}$	$\frac{1}{1}$	= 1
2-Mercaptoimidazole	„	$\frac{10}{1}$	= 10
Methylmercaptoimidazole	„	$\frac{100}{7}$	= 14

These figures of activity are those given by Stanley and Astwood (1949).

After synthesis in this country both 2-mercaptoimidazole and methyl mercaptoimidazole, which in purity were equivalent to high-grade organic analytical reagents and free from contaminants, were subjected to toxicity trials. In female mice of Schofield strain the LD50 by mouth of 2-mercaptoimidazole was approximately 2.2 g./kg. and of methyl mercaptoimidazole 0.3 g./kg. The former is of the same order of toxicity as thiouracil.

Method and Materials

A group of 18 unselected cases of thyrotoxicosis was used for this trial. Special medical record cards were prepared so that the detailed points in each case could be recorded serially. All the patients received a comp'ete clinical examination followed by measurements of arm–head circulation time (theophylline with ethylenediamine), electrocardiography (E.C.G.), *x*-ray film of chest, blood cholesterol estimation, and a radioactive iodine test. The latter was modified (Foss and Herbert, 1950) from that described by Stanley and Astwood (1948). Thyroxine synthesis was inhibited by 500 mg. of methyl thiouracil or 100 mg. of 2-mercaptoimidazole, administered one to one-and-a-half hours before a dose of 37.5 μc. of ^{131}I was given by mouth to the fasting subject. The percentage uptake of ^{131}I by the thyroid and its dissolution after a dose of 1 g. of potassium thiocyanate by mouth, given at the time of maximum concentration, were plotted against time. Figures of 12% uptake or over have been taken as evidence of toxicity, the upper limit of normal controls under these conditions being 8%. All except four of these cases had not been treated previously for thyrotoxicosis.

Treatment with 2-mercaptoimidazole was usually started with a dose of 20 mg. three times daily, and the patients were seen at intervals of up to 28 days at first and, later, when stabilized, at intervals of six to eight weeks. Each time the general clinical impression was noted, together with records of heart rate and rhythm, blood pressure, weight, neck circumference, blood cholesterol estimation, and subjective and objective evidence of toxicity or myxoedema. When necessary, further E.C.G.s were taken. In this manner a consecutive impression of the patient's reaction to treatment was formed. After progressive control of the thyrotoxicosis on the initial dose, when the patient was in a state of normal or slightly subnormal metabolism, the dose of 2-mercaptoimidazole was gradually reduced. It was intended to follow up this group for at least two years in this manner, but owing to force of circumstances this was not possible.

Of the 18 subjects originally started on this treatment three (Cases 8, 9, and 17) must be excluded, either for failing to take their tablets or for discontinuing attendance. They had all relapsed after previous courses and were not interested in further medical treatment. Brief summaries of the remaining 15 cases are shown in Table I.

Control of Thyrotoxic State

Ordinary Dosage Scheme

Twelve patients were treated with 20 mg. of 2-mercaptoimidazole three times a day, and 10 (83.3%) of these were successfully controlled (Table II). These

TABLE I.—*Case Summaries*

Case	Age	Sex	Duration of Symptoms (Mths.)	Weight Loss lb.	Thyroid Enlargement	Heart Rhythm Rate	B.P.	Eyes		Tremor	Skin	Circulation Time (secs.)	Blood Cholesterol (mg./100ml.)	^{131}I % Uptake	Remarks
								E	LR						
1	61	F	3	27*	Slight	Reg. 130	170/100	+	+	++	H.M.	7·5	164	16	Anaemia. R.B.C. 3·6 mil. Hb 76%. Some myopathy; glossitis
2	25	F	12	7	Moderate	Reg. 90	140/80	+	N	±	C.M.	8	150	28	Irritable
3	40	F	9	0	Slight	Reg. 100	160/100	+	+	+	C.M.	10	184	20	Strong family history of thyrotoxicosis
4	54	F	18	52	Moderate	A. Fib. 270–300	230/120	N	N	+	H.M.	10	190	17·5	Irritable. Early failure
5	30	F	8	24	„	Reg. 100	150/80	++	+	±	C.D.	9	164	21	See full case history
6	46	F	3	14	„	Reg. 88	130/55	+	+	±	H.M.	14	75	16	Onset following hysterectomy
7	47	F	3	16	„	Reg. 90	130/80	N	+	+	H.M.	15	125	12	Loud bruit over thyroid
10	22	M	7	7	Slight	Reg. 88	145/65	N	+	+	H.M.	14	165	23·5	Suspect pulmonary tuberculosis. Chest *x*-ray film clear. Much psychic trauma
11	26	F	3	16	Moderate	Reg. 128	155/75	N	+	++	H.M.	9	200	23·8	Onset following examination for B.A.; involuntary muscle twitching
12	49	F	12	42	„	Reg. 134	195/90	+	+	++	H.M.	11	120	31	Early cardiac failure
13	44	F	48	35	„	Reg. 118	180/80	N	±	+	C.M.	8	205	28·6	Much psychic trauma. Thyroid bruit +
14	63	F	36	5	Moderate adenoma	A. Fib. 140	180/100	N	±	+	H.M.	18	180	19·3	Early congestive heart failure. Large heart. Goitre all her life
15	54	F	6	5	Slight adenoma	Reg. 100	160/85	N	+	+	H.M.	12	198	13	Slight oedema of ankles. Absent axillary hair. Menorrhagia
16	19	F	60	0	Very large	Reg. 110	170/80	N	±	+	H.M.	7	140	18·3	Medical treatment intermittent for 5 years. Several relapses. Mentally defective
18	33	F	6	14	Moderate	Reg. 130	150/90	+	+	±	C.M.	6·5	155	27·3	F.H. goitre and diabetes. Pregnant one month after starting therapy

E = Exophthalmos. LR = Lid retraction. H = Hot. M = Moist. C = Cool. D = Dry. N = Normal. * In conversion to metric equivalents, 1 lb. = 454 g.

TABLE II.—*Details of Dosage and Effects on Progress*

Case	Initial Daily Dose	Time Before Dose Reduced Below 60 mg./Day	Condition at this Time	Time Before Heart Rate Steady	Duration of Follow-up	Maintenance Dose at End of Follow-up	Remarks
1	60 mg.	121 days	Myxoedemic	21 days	10 months	10 mg. t.d.s.	Very well
2	60 ,,	98 ,,	Euthyroid	84 ,,	5½ ,,	10 mg. b.d.	,, ,,
3	60 ,,	84 ,,	,,	28 ,,	8½ ,,	5 mg. t.d.s.	,, ,,
4	80 ,,	100 ,,	,,	140 ,,	6½ ,,	5 mg. b.d.	Very well. Auricular fibrillation changed to normal rhythm permanently after two days
5	60 ,,		Thyrotoxic				Treatment stopped owing to toxic signs. See full case history
6	60 ,,	56 ,,	Early myxoedema	28 ,,	9½ ,,	5 mg. daily	Very well
7	60 ,,	28 ,,	Euthyroid	21 ,,	6½ ,,	2·5 mg. b.d.	,, ,,
10	60 ,,	82 ,,	,,	98 ,,	6½ ,,	10 mg. t.d.s.	Uneventful progress
11	60 ,,	168 ,,	,,	168 ,,	6 ,,	20 mg. b.d.	Very well
12	100 ,,		Early myxoedema	56 ,,	5 ,,	20 mg. t.d.s.	Additional therapy with L-thyroxine sodium 0·3 mg. daily
13	60 ,,	84 ,,	Euthyroid	28 ,,	11½ ,,	2·5 mg. b.d.	Very well
14	80 ,,	56 ,,	,,		2 ,,		Thyroid adenoma removed. Owing to flutter treatment stopped
15	60 ,,	84 ,,	Myxoedemic	28 ,,	8½ ,,	10 mg. b.d.	Very well
16	60 ,,		Hyperthyroid	252 ,,	11 ,,	20 mg. t.d.s.	60 mg. daily inadequate with big goitre; 80 mg. daily produced euthyroid state
18	60 ,,	56 ,,	Euthyroid	56 ,,	8½ ,,	10 mg. b.d.	Very well. Pregnancy progressing. Exophthalmos appeared less with pregnancy

subjects were in a state of euthyroidism (7) or definitely early myxoedema (3) when the initial dose was reduced after 28–168 days (mean 86 days). Of the two remaining patients, Case 5 was treated for only 47 days, when the drug was stopped owing to a toxic febrile illness, but during this time no real change had occurred except for a slight fall of resting heart rate from 106 to 98 a minute. A full account of this case is given under the heading of toxic effects.

Case 16 was treated ineffectively for four months on this dosage, but rapid control was established by increasing it to 80 mg. daily, when a rise of blood cholesterol from 185 to 320 mg./100 ml., and a gain of 2 lb. (0.9 kg.) in weight occurred in a month. At this time the patient showed signs of early myxoedema. She had a very large goitre and had previously received three courses of thiouracil with relapse.

Other Initial Doses

In the following three cases 80 mg. or 100 mg. daily was given.

Case 4.—A married woman aged 54 was seen on September 15, 1949. She complained of attacks of palpitation for four months, loss of weight during the preceding 18 months, nervousness and irritability for two months, and increased perspiration for five weeks; about this time she had sudden attacks of dyspnoea at night. Her appetite was small and she was languid and tired. She was well nourished, weighing 130 lb. (59 kg.), but previously had been rather obese, weighing 182 lb. (82.5 kg.). Her face was expressionless and there were no eye signs. Her skin was fine, hot, and sweaty. She had firm generalized thyroid enlargement but a loud bruit, and a neck circumference of 13½ in. (34.2 cm.). There was a coarse vibrating tremor of her hands and face, and reflexes were brisk. Heart: apex beat in sixth space in the mid-clavicular line, and first sound loud; rapid fibrillation; B.P. 230/120. There was no congestive failure. E.C.G. revealed auricular fibrillation of 270–300 a minute. *X*-ray examination showed the heart size to be within normal limits and the lung fields clear. Theophylline-ethylenediamine circulation time was 10 seconds; blood cholesterol, 190 mg./100 ml. Radioactive iodine test showed a toxic curve—17.5% uptake of ^{131}I.

The patient was admitted to hospital and treatment started with 2-mercaptoimidazole 20 mg. four times daily on September 20. After two days she felt much better and the rhythm was restored to normal, the E.C.G. showing sinus tachycardia, rate 190 a minute. At this stage a punctate irritating erythematous rash developed on the forearms. After 20 days the dose of 2-mercaptoimidazole was reduced to 60 mg. daily, and at the end of a month her weight had increased by 9%, the cholesterol to 240 mg./100 ml., and the heart rate was 108. After 77 days the bruit over the thyroid had disappeared, steady progress had been made, and her weight had increased by 15%—that is, 19 lb. (8.6 kg.). After 100 days her skin was cool; the heart rate was 96, and B.P. 205/115, so the dose was reduced to 20 mg. twice daily, and later to 5 mg. twice daily. The only possible evidence of toxicity was the rash after two days.

Case 14.—A woman aged 63, with an adenoma in the right lobe of her thyroid, auricular fibrillation, and congestive failure, was treated in hospital. After three weeks in bed on 80 mg. daily her failure was controlled; she had gained 2 lb. (0.9 kg.) in weight in spite of loss of slight oedema, and the blood cholesterol had increased from 180 to 260 mg./100 ml. When she was discharged home her skin was cool, dry, and rough, and the dose was reduced to 20 mg. three times daily. After two months treatment was stopped owing to the development of auricular flutter with a 2:1/3:1 auriculo-ventricular block. Later the adenoma was removed surgically.

Case 12.—A woman aged 49 was given 20 mg. five times daily, as she was very toxic, having lost 42 lb. (19.1 kg.) in three months, and had sinus tachycardia of 134 a minute without congestive failure. After 10 days' rest in bed on this dose her heart rate fell to 80 a minute, but she developed an acute confusional state with rapid recovery and transient amnesia. Treatment was stopped for a few days, being then continued with a dose of 20 mg. three times daily. A few more "blackouts" and brief spells of amnesia occurred, but by 84 days there was definite general improvement, a gain in weight of 13 lb. (5.9 kg.)—that is, 9%—and early signs of myxoedema, an increase in thyroid size, and a cool dry skin.

Maintenance Dose

Once a definite euthyroid or early subthyroid state was achieved doses were gradually reduced, but no rigid level can be stated. When this follow-up ceased some patients were adequately controlled after 11½ months by 2.5 mg. twice daily, whereas others—for example, Case 16—still needed 20 mg. three times daily after 11 months, and in Case 12 the dose was reduced from 100 mg. daily to 60 mg. daily with the addition of L-thyroxine sodium, 0.3 mg.

Effects of Treatment

Heart Rate and Rhythm.—The time for restoration to a normal rate was variable, being only one month in six cases but in two others five and six months. With an initial dose of 80 mg. daily one patient (Case 4) with rapid auricular fibrillation of 270–300 a minute was restored to normal sinus rhythm of 190 in two days, but it required 140 days' treatment to reduce the rate to normal. In

TABLE III.—*Showing Changes in Weight and Blood Cholesterol*

Case	Age	Initial Weight lb.	Initial Cholesterol mg. %	Months After Starting Treatment																	
				1	1½	2	2½	3	3½	4	4½	5	5½	6	6½	7	7½	8	8½	9	9½	10	11
1	61	99	164	102 310		114 350		115			121 490		117 235		121 265			121				118 180	
2	25	109	150	112 225		114 210		117 219		118 215			119 175										
3	40	98	184	107 285		108		110 315		108 265		109 220			108 230				108 220				
4	54	130	170	142 240	143		149 215		153 218			157 190			165 186								
5	30	137	164	139 170			131 160	130 200															
6	46	134	75	143 145		152		156 144		154		154					154	153			153	104	
7	47	121	125	128 360		130 220		133 277			133 235				133 305								
10	22	140	165	145 220		145 195			149 180		152 160				154								
11	26	103	200	115 240			118		119 215		123			124 185									
12	49	140	120	145 185		145 190		153 185		161 210		164 100											
13	44	105	205	105 220		111		116 285		111 200		112		114	210	115		116			117 200		120 340
14	63	128	180	130 260																			
15	54	105	198	117 270		124		127	310		129 205			127	163		129		129 205				
16	19	108	140	108 160		109 174		112 170		114 185		115 320		113 220		107 179		108 175		107 120			
18	33	116	155	120 185		126		129 200		134		140 350		144 275					158 185				

this case the dose was reduced to 60 mg. daily after 100 days as the patient had in general regained a euthyroid state.

Weight.—The increase in weight was rapid in these patients, and all except two (Cases 13 and 16) showed gains in the first month. After stabilization of the toxic state the weight either remained at a steady level or continued in a few subjects to increase by as much as 20% (Table III).

Blood Cholesterol.—Although single estimations of blood cholesterol are of little clinical value, serial readings were useful in assessing the progress of these cases during treatment. In all these subjects there were significant increases after one month, and the level became high only during the development of frank myxoedema (Table III), but the early onset of the condition was best recognized clinically.

Myxoedema.—It was usual to continue the initial dose of 2-mercaptoimidazole until a euthyroid state was maintained or there was early evidence of myxoedema. After some experience, recognition of these early signs was not difficult. Patients complained of a return of tiredness and loss of energy, a feeling of depression or irritability, sometimes nausea and sickness, or an aching in the thyroid: often a gritty sensation in the eyes, with lacrimation, was noticed. They began to feel cold, and found that hair came out easily when combed. The menstrual loss occasionally became heavier. The diagnosis of the early myxoedemic state was perhaps more readily apparent to an observer who saw the patients at regular intervals. There was slight puffiness of the face, suffusion of the conjunctivae and lacrimation, dryness of the skin, and very soon a husky timbre to the voice. Often the heart rate took several weeks to reach normal after this clinical state was evident. The hair tended to become thin and the nails were sometimes brittle.

Toxic Effects

When considering signs of toxicity one had to be cautious of symptoms due to the thyrotoxic state itself, symptoms referable to cardiac arrhythmia or early failure, anxiety, early myxoedema, or some other unrelated condition. Twelve patients were free from any complaints due to drug toxicity; many of these, however, showed symptoms of early myxoedema at some stage of observation, and one had nausea, which proved to be due to pregnancy. None of this small series complained of sore throat, nor was drug fever seen in any of those treated as in-patients. From the clinical aspect the likely toxic effects can be divided into:

1. *Possible Toxic Effects* (two cases = 13.3%).—*Rash:*—Case 4, described above, had an irritative erythematous rash over the forearms, while she was sweating profusely on the second day of treatment in bed. When the dose was continued the rash cleared. *Arrhythmia:*—Case 14, described above, had auricular flutter with an adenoma. This patient had previously had fibrillation. It was thought advisable to stop treatment, and later the adenoma was removed.

2. *Probable Toxic Effects* (two cases = 13.3%).—*Confusional state and transient amnesia:*—In Case 12, described above, the episodes lasted for only a few hours while the patient was taking 100 mg. daily, with briefer "blackouts" later when on 60 mg. daily. As she had not prevously complained of similar phenomena it was presumed that the drug was responsible.

Case 5: Polyarteritis Nodosa

A married woman aged 30 was seen on July 14, 1949. She had always been nervous, and had noticed prominence of both eyes nine months previously, during which time she had lost 14 lb. (6.35 kg.). She was extremely active and was always busy. Her appetite was very large; she preferred cold weather, but did not perspire unduly, and had only occasional attacks of palpitation. She had had scarlet fever as a child. Her menses had become scanty, lasting four days every 28–30 days. She had a daughter aged 2 years. There was no family history of thyroid disease.

She was fairly well nourished, weighing 137 lb. (62.1 kg.). There was considerable bilateral exophthalmos and lid retraction. Her thyroid was full and soft; neck circumference 14½ in. (36.8 cm.). Her skin was cool and dry, with pigmentation of the

upper lids. The reflexes were brisk and a trace of coarse tremor of the hands was seen. Heart: apex beat in fifth space in the mid-clavicular line, first sound forceful; rate 100 a minute; rhythm regular; B.P. 150/80. E.C.G. and *x*-ray film were normal; theophylline–ethylenediamine circulation time 9 seconds; blood cholesterol 184 mg./100 ml. Iodine, which had been given for seven months by her doctor, was stopped and a radioactive iodine test was carried out a month later. This gave a toxic curve; also the clinical signs of toxicity were now exaggerated. Uptake of $^{131}I=21\%$.

Treatment as an out-patient was started on August 15 with 2-mercaptoimidazole, 20 mg. three times a day. After four weeks she had gained 1% in weight, with slight general improvement; heart rate 106.

After 47 days she had a pyrexial attack with generalized aches, pain in her legs, and some swelling of the ankles. Her doctor stopped 2-mercaptoimidazole and kept her in bed for 14 days. When seen after 73 days she had lost 8 lb. (3.63 kg.) in weight. The heart rate was 98 and regular, no abnormalities were found, and there was no oedema. In view of the complaint of previous pain in the legs, her reflexes and sensation were tested and found to be normal. The E.C.G. was unchanged. Treatment was resumed with 2-mercaptoimidazole, 20 mg. three times a day.

On the 87th day her condition was unchanged subjectively; her weight was the same; her neck measured 13¼ in. (33.7 cm.); the heart rate was 90, rhythm regular, and the first sound was quieter; B.P. 130/75. She complained of slight swelling of her ankles at night. Reflexes and sensation were normal. Her urine was clear; the blood cholesterol was 200 mg./100 ml. Owing to temporary shortage of 2-mercaptoimidazole, she was given methyl thiouracil, 100 mg. three times a day, which she took for two days and then developed tingling in her fingers. Four days later she was admitted to hospital obviously ill. She had signs of peripheral neuritis, with paraesthesia of hands and feet, and some weakness of the small muscles of the hands with diminished reflexes. Her thyrotoxic symptoms were, however, under control: the thyroid was normal in size, the neck circumference 12¾ in. (32.4 cm.), and the exophthalmos unchanged. Examination showed: E.S.R., 45 mm. in one hour; Hb, 90% (13.3 g.); W.B.C., 26,000 per c.mm. (neutrophils 82%). Urine contained a trace of albumin with one or two red cells and a few granular casts. She had some pyrexia and tachycardia. A diagnosis of polyarteritis nodosa was made. The peripheral neuritis progressed rapidly and there was considerable wasting of both arms and legs, with bilateral foot-drop and loss of sensation.

No definite nodules were felt and a muscle biopsy failed to show conclusive evidence of polyarteritis. She was afebrile after three weeks, and the tachycardia settled from 110–160 to 80–90 in four weeks, but by this time her B.P. was 150/120.

When she was discharged from hospital on the 184th day (91 days after admission) there was little improvement in the motor or sensory changes. Heart rate was approximately 110; W.B.C. normal. Her thyroid was normal in size and exophthalmos was definitely less. She was last seen on the 248th day, when she had increased slightly in weight and was able to walk with aid. Her neck measurement was 13½ in. (34.3 cm.); thyroid bruit was absent; heart rate 120; rhythm regular; B.P. 170/110. There was no definite evidence of thyrotoxicosis.

White Cell Counts.—White blood cell estimations were not made as a routine, but only if patients complained of any symptoms that might be attributable to the drug, and in no case was a leucopenia found.

Discussion

The number of cases in this series is too small and the duration of treatment too short for one to form more than an impression of the efficacy of 2-mercaptoimidazole in the doses used to control the thyrotoxicosis. In most patients a dose of 60 mg. daily would seem to be adequate, 10 out of 15 cases (66.6%) were successfully controlled. In three other subjects control was achieved by 80 mg. daily, and another patient required 100 mg. daily. The remaining case was not long enough on the drug for the adequacy of 60 mg. daily to be judged, as toxic signs appeared and treatment was stopped. In general these findings agree with those of Stanley and Astwood (1948).

In Cases 5 and 14 the drug was stopped owing to possible toxic reactions, and in Case 16 it was decided to remove a very large goitre. The remaining 12 patients were adequately controlled on maintenance doses for periods of 5 to 11½ months.

It is unlikely that the rash which appeared within two days of treatment in Case 4 was due to the drug, as she was sweating profusely, and it was irritative and confined to the forearms Further, it disappeared with the continuance of treatment. The change of rhythm from auricular fibrillation to flutter is a doubtful toxic manifestation and is not mentioned in the literature.

It is interesting that the two probable toxic reactions were neurotoxic. Frawley and Koepf (1950) discuss the neurotoxic manifestations described in the literature in relation to thiouracil, methyl thiouracil, propyl thiouracil, and cyclopropyl thiouracil, although, according to Bartels (1948), they constitute only an almost negligible fraction (1.8%) of the total toxic reactions. Confusional states, aural and visual hallucinations, and even toxic psychoses have been seen after thiouracil; numbness of the extremities, vertigo, paraesthesia, and loss of taste after methyl thiouracil; and tingling in the tip of the tongue, numbness of the lips, a burning sensation in the throat, pain in the jaws and facial muscles, and emotional disturbances after propyl thiouracil.

Frawley and Koepf postulate that as thiouracil derivatives depress the peroxidase enzyme system of the thyroid, they may well interfere with other enzyme systems necessary for function of the nervous structures. These authors state that the neurotoxic manifestations may be the first, the sole, or the most pronounced evidence of intoxication with these drugs.

Although a confident clinical diagnosis of polyarteritis nodosa was made in Case 5, it was not proved by muscle biopsy. Astwood (1949—personal communication) had heard of another possible case in his series, then enlarged to 50 cases, treated with 2-mercaptoimidazole, but that case was not under his immediate supervision at the time.

Although the incidence of two cases (13%) showing neurotoxic signs is relatively high, this series is far too small for an assessment to be made, and the true perspective is probably to be obtained from Bartels's (1948) statement that the incidence is really extremely low—1.8% of all toxic reactions. Because of its high activity/toxicity ratio in animals, and this confirmation of Astwood's data, 2-mercaptoimidazole merits extended clinical use in thyrotoxicosis.

Summary

2-Mercaptoimidazole was used for treatment of 15 unselected cases of thyrotoxicosis during periods of 5 to 11½ months.

A dose of 60 mg. daily was found adequate to control the condition in 66.6%. In three other subjects control was achieved by 80 mg. daily. A fourth patient required 100 mg. daily, and the remaining case was not treated.

One patient developed polyarteritis nodosa after 47 days' treatment, otherwise toxic reactions were few and of fleeting and mild nature.

I am greatly indebted to Professor C. B. Perry for his interest, advice, and encouragement; to those members of the consulting staff of the Bristol Royal Hospital who referred cases; and to Dr. Russell Fraser for his criticism. Supplies of 2-mercaptoimidazole were kindly

provided by British Schering Ltd., to whom I am also grateful for data on the animal toxicity.

REFERENCES

Astwood, E. B. (1943a). *J. Amer. med. Ass.*, **122**, 78.
—— (1943b). *J. Pharmacol.*, **78**, 79.
Bartels, E. C. (1948). *J. clin. Endocrinol.*, **8**, 766.
Foss, G. L., and Herbert, R. (1950). In press.
Frawley, T. F., and Koepf, G. F. (1950). *J. clin. Endocrinol.*, **10**, 623.
Stanley, M. M., and Astwood, E. B. (1948). *Endocrinology*, **42**, 107.
—— —— (1949). Ibid., **44**, 588.

INTRAVENOUS IRON IN TREATMENT OF HYPOCHROMIC ANAEMIA ASSOCIATED WITH RHEUMATOID ARTHRITIS

BY

R. J. G. SINCLAIR, M.R.C.P.Ed.

Assistant Physician, Rheumatic Unit, Northern General Hospital, Edinburgh

AND

J. J. R. DUTHIE, F.R.C.P.Ed.

Lecturer in Rheumatic Diseases, Department of Medicine, University of Edinburgh

In a previous communication (Sinclair and Duthie, 1949) we reported the results following the administration of intravenous iron in 23 cases of rheumatoid arthritis with hypochromic anaemia. These cases have now been followed up for periods varying from 7 to 23 months. A further 28 cases have been studied in respect of the haemoglobin response and changes in the erythrocyte sedimentation rate (E.S.R.) following 1 g. of intravenous iron. Iron absorption has been measured in seven cases. In four cases large doses of ascorbic acid have been given in order to assess its effect on the utilization of iron.

Haemoglobin percentages were estimated by a photoelectric colorimeter graduated to register 14.8 g. Hb per 100 ml. as 100%. Westergren tubes were used to measure the E.S.R. Wintrobe's dry mixture of ammonium and potassium oxalate served as an anticoagulant. No correction for anaemia was made, as no reliable method is available. Davis (1946) states that correction for anaemia is usually unnecessary if the Westergren method is used, and that such correction may lead to fallacious results. The moderate degree of anaemia present in most cases of rheumatoid arthritis would be unlikely to influence the E.S.R. to any significant extent.

Results

Follow-up of First Series.—Of the original 23 cases 16 responded to intravenous iron ("ferrivenin"), and seven remained refractory. Of the 16 cases that showed a satisfactory rise in haemoglobin percentage 13 have maintained this level without further iron for periods varying from 7 to 23 months. In the remaining three cases the initial response was not maintained; but all three responded to a second course. Details are given in Table I. Of the seven refractory cases, three received a second course without effect.

Results in Second Series.—Twenty-eight new cases have been given courses of intravenous iron. All were subjected to the same basic regime as the original cases and showed no significant response to oral iron for one month. In 14 cases the preparation used was ferrivenin. A test dose of 50 mg. was followed by 200 mg. daily for five days. In the remaining 14 cases "iviron" was used. A test dose of 200 mg. was followed by 400 mg. daily for two days. Mild toxic symptoms were encountered occasionally with both preparations. These have become very much less frequent since all-glass syringes were adopted in place of glass and metal syringes. In 22 cases a good haematological response was obtained. The average haemoglobin percentage in these cases on admission to hospital was 70. After one month on oral iron it was 71.8. One month after 1 g. of intravenous iron the average figure was 84.3. At three months the average figure was 87.1. In the remaining six cases in this group the response was poor or absent.

TABLE I.—*Follow-up of 16 Cases with Good Haemoglobin Response to Intravenous Iron*

Case No.	Haemoglobin %			
	After 1 Month on Iron by Mouth	Response to Ferrivenin 1·05 g. Intravenously		
		1 Month After Injection	Final Level	Time in Months
1	79	83	96	13
2*	66	87	90	13
3	72	92	92	9
4	68	80	100	23
5	71	90	90	11
6	74	96	96	14
7*		65	84	12
8	76	88	96	17
9	65	78	82	9
10	70	82	93	7
11*	63	83	93	10
12		76	86	13
13	82	97	96	9
14	75	90	96	16
15		75	84	7
16	80	92	100	15

* Required second course.

Iron Absorption.—To ascertain whether faulty absorption of iron from the gut might explain the failure of these patients to respond to iron by mouth, serum iron values were measured after the administration of 18 gr. (1.2 g.) of ferrous sulphate in seven cases. The method used was that described by Dahl (1948). The results are shown in Table II. In all seven cases serum iron values and absorption curves fell within the normal range. In six cases the response following the administration of 1 g. of iron intravenously was satisfactory. In one case no rise in the haemoglobin level followed the administration of a total of 2 g.

TABLE II.—*Serum Iron Absorption (7 Cases)*

Time	Serum Iron Levels μg. per 100 ml.						
10 a.m. (before oral iron) ..	90*	83	66	89	90	75	94
12 noon (after 18 gr. oral iron)	200	126	—	166	150	83	146
2 p.m. " " " "	210	250	200	116	150	110	155
4 p.m. " " " "	160	83	56	106	80	96	103

* In spite of good absorption curve there was no appreciable rise in haemoglobin level following two courses of intravenous iron.

Erythrocyte Sedimentation Rate.—A fall in E.S.R. was noted in cases responding to intravenous iron in the first series of cases studied. This point has now been investigated in more detail. In 10 cases the E.S.R. was measured daily during the course of injections. The results are given in Table III. It will be noted that in six cases showing a good response the E.S.R. fell sharply, while in the four refractory cases there was no significant alteration in rate. Five cases were selected in which haemoglobin values were 80% or over but in which the E.S.R. was markedly raised. After 1 g. of intravenous iron the rate fell and the haemoglobin percentage rose in all five (Table IV). In Case 5 the

TABLE III.—*The E.S.R. in 10 Cases Responding to Intravenous Iron*

Case No.	E.S.R. (mm. in 1 Hour)				Initial Hb%	Final			Response
	Before 1st Injection	Before 2nd Injection	Before 3rd Injection	1st Day After 3rd Injection		Hb%	E.S.R.	Time in Days	
1	100	39	29	60	57	99	25	50	Good
2	37	21	4	25	78	90	12	19	,,
3	73	38	65	64	60	84	48	30	,,
4	35	33	17	24	79	96	40	67	,,
5	100	100	40	—	69	89	62	24	,,
6	45	35	34	5	76	91	28	49	,,
7	103	102	98	96	66	72	72	59	Poor
8	60	—	96	90	72	79	84	25	,,
9	78	69	69	—	72	75	72	15	,,
10	95	90	97	115	78	70	110	32	,,

TABLE IV

Case No.	E.S.R. (mm. in 1 Hour)			Initial Hb%	Final		
	Before Injection	After Injection	Time in Days		Hb%	E.S.R.	Time in Days
1	90	52	6	87	100	24	102
2	72	40	4	81	96	33	146
3	60	23	11	80	95	42	29
4	70	27	7	81	97	16	90
5	60	48	7	82	97		
5*	90	45	3	78	90	28	133

* Second course.

fall in E.S.R. was only moderate. In five weeks the haemoglobin level fell and the E.S.R. rose again. A second course brought a more marked fall in E.S.R. Haemoglobin percentage rose to 90 and has been maintained at this level.

Effect of Ascorbic Acid.—The plasma ascorbic acid in rheumatoid arthritis is often subnormal (Rhinehart *et al.*, 1937). Tötterman (1949) could find no correlation between plasma ascorbic acid values and the ability of the organism to utilize iron. It was felt, however, that the point was worthy of further investigation. Four patients were given 1 g. of ascorbic acid intravenously on three successive days. There was no significant change in the E.S.R. or haemoglobin percentage. Seven days later the same patients were given 1 g. of ascorbic acid along with each of three injections of iviron (total 1 g.). The fall in E.S.R. and the rise in haemoglobin levels were of the same order as those which followed intravenous iron alone.

Effect of Intercurrent Infection.—A patient whose response to intravenous iron had been good (haemoglobin rose from 80% to 91%) developed a large abscess in the gluteal region. The haemoglobin dropped to 79% in the course of three weeks. The abscess was opened and drained, and the haemoglobin rose to 89% without further iron. The infection recurred, and the haemoglobin again fell to 79%. When healing finally took place the haemoglobin rose to 90% and the E.S.R. dropped from 70 to 20 mm. in one hour.

Subjective Responses.—The majority of patients who eventually show a good response to intravenous iron remark on a feeling of increased well-being and improved appetite immediately after the course of injections, before there has been any change in the haemoglobin level.

Discussion

The response to intravenous iron has now been studied in 51 cases of rheumatoid arthritis with hypochromic anaemia, proved to be resistant to iron by mouth in adequate doses. A satisfactory rise in haemoglobin level was shown in 38 cases; and 13 remained refractory. Of the latter, eight have received a second course, but only two have responded.

Hypochromic anaemia is a common complication of many chronic infections, and in the past has often been ascribed to a toxic depression of the marrow. It has been presumed that the anaemia in rheumatoid arthritis belongs to this group, though the aetiology of the disease remains obscure. Anaemia due to a toxic depression of the marrow would not be expected to respond to iron given by any route. The fact that a significant number of cases do respond when iron is given intravenously in large doses suggests that the anaemia is due to an increased need of the tissues for iron. This demand apparently cannot be met by the oral administration of iron, even though absorption from the gut is normal. Vannotti and Delachaux (1949) and Tötterman (1949) have both shown that in the presence of infection iron given intravenously is rapidly removed from the blood. It is only since preparations of iron which can be given intravenously in large doses became available that it has been possible to show that haemoglobin levels can be restored to normal in some cases completely resistant to iron given by mouth. It seems reasonable to presume that it is only when the needs of the tissues have been met that an excess of iron becomes available for the formation of haemoglobin in these cases. Iron utilization does not appear to be favourably influenced by the administration of large doses of ascorbic acid.

The striking fall in E.S.R. which has been observed in those cases responding to intravenous iron requires further investigation. No readily acceptable explanation presents itself. An increase in the E.S.R. is closely related to alterations in the pattern of the serum proteins (Ham and Curtis, 1938). Detailed studies of the serum proteins before and after the administration of iron by the intravenous route may shed some light on this problem.

Summary

Intravenous iron was given to 51 cases of hypochromic anaemia associated with rheumatoid arthritis. These cases had all proved resistant to oral iron.

A satisfactory rise in haemoglobin levels was shown in 38 cases.

Thirteen cases remained refractory. Eight of these were given a second course, but only two showed a response.

Twenty-three cases have been followed for periods of 7 to 23 months. Haemoglobin levels have been maintained in 13 of these cases without further iron. Three cases which responded initially required a second course.

Iron absorption was measured in seven cases and was found to be within normal limits.

Cases responding to intravenous iron show a rapid fall in E.S.R.

Ascorbic acid does not materially improve the response to intravenous iron.

It is suggested that in rheumatoid arthritis there is a marked increase in the need of the tissues for iron. Only when this need is met by large doses of iron intravenously does iron become available for the formation of haemoglobin.

We are indebted to Professor L. S. P. Davidson for valuable criticism and advice, and to Dr. J. L. Potter, who was largely responsible for the haematological investigations. While this work was in progress the Rheumatic Unit, Northern General Hospital, was in receipt of a grant from the Nuffield Foundation. Iviron was kindly supplied by British Schering Ltd.

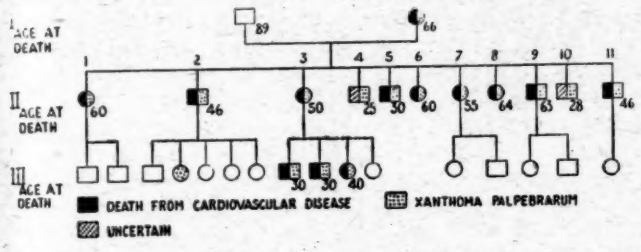
REFERENCES

Dahl, S. (1948). *British Medical Journal*, **1**, 731.
Davis, L. J. (1946). *Practitioner*, **157**, 13.
Ham, T. H., and Curtis, F. C. (1938). *Medicine*, **17**, 447.
Rhinehart, J. F., Greenberg, L. D., Baker, F., and Choy, F. (1937). *J. Amer. med. Ass.*, **109**, 1394.
Sinclair, R. J. G., and Duthie, J. J. R. (1949). *Lancet*, **2**, 646.
Tötterman, L. E. (1949). *Acta med. scand.*, **134**, Suppl. 230.
Vannotti, A., and Delachaux, A. (1949). *Iron Metabolism and Its Clinical Significance*. Muller, London.

Medical Memoranda

Xanthoma Palpebrarum and Cardiovascular Disease

The accompanying family tree, which is self-explanatory, may prove interesting. The conjunction of xanthoma palpebrarum and cardiovascular disease in three generations seems remarkable in view of the wide distribution



of cholesterol in the tissues and the variety of disease syndromes that could accompany disturbance of lipoid metabolism.

Nine members of the second generation were victims of cardiovascular disease. The two remaining brothers had heart disease, but one died from diphtheria, and the information available regarding the other is not sufficient to enable me to be definite about the cause of death.

Sir John Parkinson saw No. 8 five years before her death. He has kindly allowed me to quote from his report and from a later full review of the cardiovascular aspects of the case. I am taking advantage of his offer so as to make this patient's cardiovascular picture clear, and so give a good idea of the disease as it affected the other members. The uniformity of symptoms throughout the group is striking. Sir John notes: "For a few years Mrs. X has been more breathless on exertion, and for 18 months she has also had an upper sternal pain extending into the left arm. This is related to exertion or excitement, and otherwise she is pretty well. Signs on examination are few. The blood pressure is 150/80. Radiographs show no cardiac enlargement. The electrocardiogram does point to coronary disease." In a later review of the case he writes: "It was my opinion that your patient, Mrs. X, had angina of effort. The electrocardiogram shows in Lead I some R–T depression with a diphasic T wave; there is a corresponding S–T elevation in Lead III. This combination, with slight widening of the QRS, seen best in Lead II, points to coronary disease. There was no evidence that she had hypertension then."

Two years later her blood pressure rose and for a time remained at 200/100 and her cardiac reserve fell further, pain coming on slight exertion and sometimes wakening her at night. Her blood pressure later fell to 150/100. She died from coronary thrombosis.

Of four sibs of the third generation, one had extensive xanthoma palpebrarum, angina, dyspnoea on exertion, and hypertension. Symptoms increased slowly over 10 years. Death occurred from coronary thrombosis. Two others had cardiac disease, and both died suddenly.

Other diseases associated with hypercholesterolaemia were not in evidence, nor was any extension of the xanthoma noticed except in Case 8, in which yellow glistening patches appeared under the mucous membrane of the underside of the tongue, accompanied by superficial glossitis. Her cholesterol was 345 mg. per 100 ml., and the Wassermann reaction was negative. In a member of the third generation presenting no clinical signs or symptoms the cholesterol is 230 mg. per 100 ml.

I am grateful to Sir John Parkinson for the use of his reports, and to Dr. Vaughan Facey for reports and cholesterol estimations, and permission to use them.

P. P. MCKINNEY, M.B.

BIBLIOGRAPHY

Darier, J. (1928). *Précis de Dermatologie*, 4th ed., p. 1015. Masson, Paris.
Engelberg, H., and Newman, B. A. (1943). *J. Amer. med. Ass.*, **122**, 1167.
Jones, E. S., and Robertson, P. W. (1948). *British Medical Journal*, **1**, 1137.
MacKenna, R. M. B. (1948). *Modern Trends in Dermatology*. Butterworth, London.
O'Leary, P. A., and Montgomery, H. (1947). *Coll. Pap. Mayo Clin.*, **39**, 374.
Weber, F. P. (1948). *British Medical Journal*, **1**, 1254.

Acute Volvulus of the Stomach

Volvulus of the large intestine is fairly common, volvulus of the small intestine is much rarer, while volvulus of the stomach is very uncommon.

In 1927 Laeven summarized 40 cases of volvulus of the stomach, since when very few additional cases have been recorded. In a review of the literature the following points are stressed: (1) ptosis of the stomach with laxity of its ligaments causing a greater distance between the diaphragm and the stomach; (2) gastric disturbance associated with excessive peristalsis; and (3) congenital weakness of the left side of the diaphragm.

CASE REPORT

A man aged 42 was admitted to hospital on January 3, 1945, complaining of agonizing pain in the upper epigastric region. It had started about four hours before admission whilst he was drinking a glass of beer. He had had stomach pain and flatulence after meals for 12 months.

On examination the appearance of the abdomen was striking, it looked as if he had a football within the upper part of his peritoneal cavity. The rest of the abdomen was of normal size. As the patient was in agonizing pain, a large dose of morphine was given and arrangements were made for an immediate laparotomy. The pulse was 80 and the temperature 97° F. (36.1° C.). The swelling was resonant on percussion. Various diagnoses were made, the nearest being that of volvulus of the large intestine.

Operation.—The abdomen was opened by a left upper paramedian incision under general anaesthesia, and a large tense gaseously distended swelling the size of a football was found. The stomach was seized with ¼-in. (1.25-cm.) Duval forceps and a large trocar inserted to relieve the gaseous distension. After all the gases had escaped, the gastric puncture was closed. It was then found that the pyloric end of the stomach, which was very movable, was twisted anteriorly and to the left, lying in the left flank by the spleen, whilst the cardiac end and the adjoining oesophagus was wound round the pylorus and was under the right costal margin. The stomach was twisted and obstructed at both the cardiac and pyloric ends.

After the gastric distension had been relieved the volvulus of the stomach untwisted itself in an anticlockwise direction, which brought it into its correct position. The Duval forceps which had been applied to the stomach and were lying to the left of the abdomen suddenly moved towards the right side. The volvulus had been cured by the simple process of relieving the gastric distension. The anterior part of the stomach was fixed to the anterior peritoneal wall and the abdomen was closed in layers. For several days the abdomen remained very distended and a Ryle's tube was kept in the stomach to relieve this.

Three weeks later the patient left hospital quite well. A small incisional ventral hernia had to be cured twelve months later. He has remained well ever since, has had no symptoms, and has been able to resume his work as a full-time fitter.

P. QUINET, F.R.C.S.Ed.

Reviews

RECENT PHARMACOLOGY

Recent Advances in Pharmacology. By J. M. Robson, M.D., D.Sc., F.R.S.Ed., and C. A. Keele, M.D., F.R.C.P. (Pp. 418; 46 illustrations. £1 4s.) London: J. and A. Churchill. 1950.

Pharmacology still holds an insecure place in the medical curriculum in this country. The reasons for this are varied, but probably the most important is that the people who are now senior physicians and surgeons often found their study of pharmacology unprofitable. The result is that they are anxious to-day to keep the course short and therefore superficial.

All interested in the development of medicine in Britain would do well to spend an hour or two looking at this book by Professor Robson and Dr. Keele. They would realize how closely pharmacology is bound up with the most important aspects of medical research, and how badly fitted to advance medicine is anyone whose knowledge of pharmacology is slight. They might well wonder how far teachers of pharmacology have time to cover the subject as it is dealt with in the book, and they might further wonder whether the study there outlined might not take the place of some of the matter taught in allied sciences.

It is difficult to convey the excellence of this book by mentioning the subjects considered. The last chapter illustrates the use of medical statistics by examining in detail the evidence put forward by the Medical Research Council's committee for the value of streptomycin in pulmonary tuberculosis, and also the evidence of Wright and his colleagues for the value of anticoagulant therapy of coronary thrombosis with myocardial infarction. In this chapter the medical student can learn all he needs to know about statistics. Yet at the present time in some medical schools statistics is being taught as a special subject. Those who read this chapter will see how well the pharmacologist can do it.

The great merit of the book is that all the complicated subjects which have recently come into medicine—as, for example, the use of tracer elements—are explained with great simplicity. The chapter on radioactive isotopes is an excellent short introduction to this subject, containing illustrations very well chosen. The chemotherapy of malignant disease, mutagenic substances, the haemopoietic system, the steroids of the adrenal cortex, and antimalarial substances are all described with evident care for accuracy.

Pharmacologists themselves owe a great debt to Professor Robson and Dr. Keele for this work, and it is to be hoped that they will make full use of the book in their teaching. All physicians, perhaps even professors of medicine, will find it of service, and in reading it may form a different conception of the importance of pharmacology.

J. H. BURN.

RADIOGRAPHY IN SURGERY

Unfallchirurgie im Röntgenbilde. By W. Ehalt. (Pp. 619; 1,379 illustrations, 14 tables. M. 60: schillings 180; or Swiss francs 60.) Vienna: Wilhelm Maudrich. 1950.

The author of this important work is director of the accident clinic at Graz, in Austria. He was formerly for many years assistant to Professor Böhler in his famous clinic at Vienna. For 22 years he has devoted his life to the subject of fractures and other injuries of the bones, and he here presents the results of his experience both from his own clinic and from the vast records accumulated by Böhler himself. The extent of this experience may be judged from the statement that he dealt with 200,000 injured persons and with two million radiographs.

It is essentially a surgical work, although entirely on the services which *x* rays can render to surgery, and the relationship of the radiologist to the surgeon is pleasantly shown in the thanks offered by Dr. Ehalt to Professor Böhler for teaching him how to read a radiograph. The whole volume bears testimony to the immense value of such co-operation and is indeed a triumph of that art.

Although the illustrations with which the text is profusely supplied are not so perfect as those in a recent British textbook, they are sufficiently clear for their purpose, and their value to the surgeon is enhanced by the descriptive notes by which they are accompanied. Surgeons will be interested in the use made of local analgesia, apparently almost as a routine procedure. This again requires a degree of collaboration unusual in Britain. There are many excellent diagrams calling attention to special points in the radiographs. Those of the many and difficult fractures which may occur about the wrist are particularly well conceived.

The whole volume is a masterpiece and deserves most careful study. The German is clear and easy to follow, but an English translation would, we feel, meet with immediate success.

HENRY SOUTTAR.

SURGERY FOR STUDENTS

A Short Textbook of Surgery. By C. F. W. Illingworth, C.B.E., M.D., Ch.M., F.R.C.S.Ed. 5th edition. (Pp. 676; 233 figures, 13 plates. 30s.) London: J. and A. Churchill. 1950.

It is very satisfactory that a new edition of this book has been called for. Few teachers in this era of extreme specialization have a wide enough knowledge to write a textbook of general surgery, yet there is an obvious advantage to the student. There is a uniform presentation of the subject and the balance is more likely to be even than in a textbook by many authors. The problem of writing such a book is immensely increased when the author is determined to keep it to a small compass so that the student can carry it about with him and read it through several times. Professor Illingworth has faced these difficulties and overcome them successfully, as the continued popularity of the book shows.

Yet the book might be even better and more useful if some subjects such as rehabilitation, massage, gynaecology, and the surgery of the special senses had been omitted. All these subjects are taught in departments other than general surgery. There would then be more room to go into the reasons for and against different methods of treatment a little more fully. The book is a little defective in this respect, a restriction obviously imposed by the necessity for brevity.

In this edition there are new sections on surgery of the heart, portal hypertension, and infections of the fingers. We are pleased to see the revision of this last important subject. But surely it is better to give penicillin for paronychia than simply to cover it up with "elastoplast." On page 3 the author must mean saturated, not superheated, steam, which is not so effective as a sterilizing, and is often indeed a charring, agent. Curiously, in the section on thrombophlebitis the author mentions only heparin and does not seem to use dicoumarol, though this drug is mentioned on page 109.

Good features of the book are the lucid instructions for the examination of patients, and the description of the

manipulation of joints. In line 26, page 290, "frail" appears to be a misprint for "flail." But one can find only minor blemishes. Students who read this book should possess or have access to a larger treatise on surgery. They will find this book extremely useful as a basis for their wider reading.

C. A. PANNETT.

PSYCHOLOGY OF KRETSCHMER

Medizinische Psychologie. By Dr. Ernst Kretschmer. Tenth edition. (Pp. 304; 23 illustrations. M. 24.) Stuttgart: Georg Thieme. 1950.

In this textbook of medical psychology, which now appears in its tenth edition, Kretschmer gives an authoritative exposition of his school of psychiatric thought. It follows the dominant trends of German psychiatry with its emphasis on descriptive and conceptual systematization, its speculative search for basic principles, its construction of specific terminologies with fine shades of differential meaning, and its preference for the typing and classifying of individual personalities and their traits.

The cornerstone of Kretschmer's system of thought is the hypothesis that a common constitutional matrix links the phenomena of the mind not only with the functions of the brain and endocrine glands, but also with the general body structure. He assumes that, if everything were known, it would be found that a particular mind could occur only in a particular organism of defined structure and physiology. It is common knowledge to-day how far he has succeeded in supporting this hypothesis when he demonstrated that extremes of bodily physique tend to be associated with specific psychological traits or characteristic psychotic syndromes. Some of his clinical findings have since stood the test of more exacting statistical investigations, but Kretschmer's vivid delineation of schematic types will have a more immediate appeal to the psychiatric student for whom the book is intended.

The bias towards typing and constitutional predestination leads necessarily to a disparagement of environmental influences. English psychiatrists may be surprised to read that the repression of previous sexual knowledge in early puberty is biologically determined, or that a psychic trauma in infancy is not a trauma at all, but an early manifestation of constitutional trends.

The form rather than the content of mental phenomena is everywhere emphasized, for the form may have a generally valid biological basis, whereas the content would be fortuitously conditioned by individual experience. When the development of mental characteristics is considered, phylogenetic speculations about the historical past of the human race are introduced, but the historical past of the individual receives hardly any attention.

The new edition has been enlarged by an account of the work of W. R. Hess on the physiology of the brain and by a description of the "orbital lobe syndrome." The latter is based on the clinical observations of Kleist which Kretschmer could confirm and supplement, but there is no reference to the extensive non-German literature on the subject which has appeared since the introduction of prefrontal brain operations in the treatment of psychoses. A brief account has also been added of a new method of treatment termed "fractional active hypnosis." It consists in a graduated training in autosuggestive exercises, and is based on principles similar to those underlying the "autogenous training" of J. H. Schultz in Germany and the relaxation treatment of Jacobson in America.

F. K. TAYLOR.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received

Handbook of Child Health. By A. Furniss, L.R.C.P., L.R.C.S.Ed., L.D.S., D.P.H. (Pp. 280. 25s.) London: Sylviro Publications. 1950.

John Ferriar: William Osler. By E. M. Brockbank, M.B.E., M.D., F.R.C.P. (Pp. 51. 6s.) London: William Heinemann. 1950.

The Walker Trust Lectures on Leadership, 1930-49. (Pp. 282. 15s.) London: Geoffrey Cumberlege. 1950.

The Inner World of Man. By Frances G. Wickes. (Pp. 344. 21s.) London: Methuen. 1950.

Maternity Care in Two Counties. By F. E Whitacre, M.D., and E. Whiteman Jones, M.P.H. (Pp. 165. 4s.) London: Geoffrey Cumberlege. 1950.

A Guide to Medicine. By I. Geikie-Cobb, M.D., and various contributors. (Pp. 416. 15s.) London: George G. Harrap. 1950.

Handbook for Photofluorographic Operators. Prepared by the Division of Tuberculosis of the Bureau of State Services. Public Health Service Publication No. 18. (Pp. 69. 45 cents.) Washington, D.C.: United States Government Printing Office. 1950.

L'Oxyde de Carbone et l'Oxycarbonisme. By Professor V. Raymond and A. Vallaud. (Pp. 367. 500 francs.) Paris: Institut National de Sécurité pour la Prévention des Accidents du Travail et des Maladies Professionnelles. 1950.

Einführung in die Hals-Nasen-Ohren-Heilkunde. By P. Falk, M.D. 2nd ed. (Pp. 175. M. 19.80.) Stuttgart: Georg Thieme. 1950.

Physiologie und Pathologie des Bilirubinstoffwechsels als Grundlagen der Ikterusforschung. By Tr. Baumgärtel, M.D. (Pp. 271. M. 27.) Stuttgart: Georg Thieme. 1950.

Die Sexualität bei Tuberkulösen. By H. Westermann, M.D. (Pp. 30. M. 2.70.) Stuttgart: Georg Thieme. 1950.

Die Tuberkulose der Haut. By Professor K.-W. Kalkoff. (Pp. 93. M. 7.80.) Stuttgart: Georg Thieme. 1950.

Klinische Physiologie und Pathologie. By F. Hoff, M.D. (Pp. 782. M. 39.) Stuttgart: Georg Thieme. 1950.

Lehrbuch der Inneren Medizin. Edited by H. Dennig. Vol. 2. (Pp. 1,117. M. 39.) Stuttgart: Georg Thieme. 1950.

Did Adelaide Bartlett . . . ? (Christopher Johnson, London; 9s. 6d.) is the first of a series which the publishers are bringing out under the title of "Medical Viewpoint," and it sets a high standard in entertainment. The author, whose pseudonym is said to mask the name of a well-known specialist in anaesthetics, has written a lively account of the events which led to a notorious murder trial in 1886. Adelaide Bartlett was a "small, slim, nicely bosomed brunette," whose husband—a prosperous grocer—died one night in their Pimlico flat from chloroform poisoning. Adelaide was accused of his murder, and "over every teacup and tankard in the kingdom" discussion raged about how the poison got into the victim's stomach. The case gained notoriety from the fact that a young Methodist minister formed the third person in a rather unusual triangle. The book which Gordon Gwynn has written about these real characters is much brighter than most crime fiction, for his wit illuminates the many amusing facets of Victorian life as well as enlivening the slow and inevitable march of justice in a British court. Naturally he uses his special knowledge to discuss the medical evidence which was given at the trial, but the reader feels that the pages he really enjoyed writing were those in which he describes with wicked gusto the commonplace foibles of ordinary people. The author's patients are fortunate if he can pass an endotracheal tube as neatly as he can turn a phrase.

BRITISH MEDICAL JOURNAL

LONDON

SATURDAY DECEMBER 2 1950

A FAILING POLICY

Just in what direction is the National Health Service heading? The outside observer, ignoring our capacity—which one day might be exhausted—for muddling through, would be justified in saying, "For the bankruptcy court." Not only are we facing bankruptcy because of the Utopian finances of the Welfare State. We are, as a profession, facing the bankruptcy of a policy, a policy based on the decisions of the Coalition Government during a war for survival and put into execution by a Minister of Health who could not resist the temptation to behave like a Fairy Godmother to an impoverished nation. A foreigner, past the age of being able to subscribe to the social security services, can stay in this country for a few months and then get a set of dentures, two pairs of spectacles, and a completely free medical service without having contributed a farthing's worth of work or of money. While the money spent in this way may be only a drop in a bucket leaking at the bottom and overflowing at the top, the instance nevertheless illustrates the grandiloquent irresponsibility of those who in a rash of paternalism have so thoughtlessly squandered other people's money.

There were two main themes in the National Health Service which appealed to many medical men apart from any views they may have held about the practicability of a comprehensive medical service for the nation after a long and impoverishing war, and apart from the grave doubts they may have entertained about the wholesale intrusion of the State into personal medical services for the sick.

The breathless advances of medical science had left the general practitioner, working on his own, in partial isolation. After the 1914–18 war Lord Dawson had already sensed this, and had suggested as a remedy the practice of general medicine from health centres. The idea of health-centre practice commended itself to the Planning Commission set up by the B.M.A. in the early years of the war of 1939–45. The Health Centre became, by adoption, the principal plank in Mr. Bevan's platform for general practice. From this all sorts of tempting benefits to the general practitioner were supposed to flow: regular hours, regular holidays, co-operative work in a group, all the aids of modern medicine at hand, night shifts, secretarial assistance. Here indeed was the promise of a brave new medical world in which brightly burnished *x*-ray installations in the health centre would relegate the stethoscope to the museum of medical curiosities. The general practitioner has been promised greater opportunities in the hospital life of the country: what has happened at Kingston is fitting comment on this. As to payment, a new deal was promised in the shape of the Spens Committee's recommendations, which advocated a spread of income, adjusted to the current value of money, among certain proportions of general practitioners. Now, two and a half years after the appointed day of July 5, 1948, this adjustment is still the subject of miscalculation, postponement, and evasion by the Minister of Health. The financial maladministration of the Health Service has compelled the Chancellor of the Exchequer to say, "Not a penny more!" But this does not excuse the failure to define what should be the terms of fulfilment of the Spens recommendations, even though the circumstances of the country may make it difficult to meet them here and now. The medical profession does not cry for the moon. It asks simply for a clear definition of a contract. On both the medical and the economic front the Minister of Health has failed to do all those things he promised to do for the efficient supply of general medical services to the public.

The recent circular of the Ministry of Health on registrars[1] underwrites the second failure of the Minister, driven though he may be to this by a directive from the Treasury. But the failure nevertheless is his for indulging in fantasies of extravagance. What won over to the National Health Service a large body of consultants between 1945 and 1948 was the promise of an evenly distributed consultant service in the length and breadth of Britain, and an ever-widening opportunity for the young and able to man this service without the financial discouragement and disability that had prevailed in the wicked and recent past. Here was the new charter for the patient in the neglected wilds of the provinces and for the young consultant eager to win his spurs, gilt-edged with the promise of a merit award. And now, just two and a half years after these bright visions were held out before the young, 1,100 out of 2,800 registrars are told they must look elsewhere. The Minister of Health faces the bankruptcy of a policy in the consultant as well as in the general medical services. And what must astound the historian of the future is the failure in what is termed a "Health Service" to enlarge and encourage the Public Health Service, the members of which have perhaps had the hardest knock of all.

[1] *Supplement*, Nov. 18, p. 204.
[2] *The Times*, June 18, 1948.
[3] *British Medical Journal*, 1949, 1, 293.

On all the three main fronts of the National Health Service the Minister of Health's policy is failing. The honeymoon period of the Welfare State is over. The uneasy marriage between the medical profession and the State is now undergoing the strains of an unbalanced domestic economy. The National Health Service, if it is not to fail completely in its aims, will, we are convinced, have to undergo successive modifications in the next few years. The British Medical Association, it must be recalled, expressed in the years between 1945 and 1948 its "whole-hearted desire" for a comprehensive medical service for the whole of the nation. It did not discriminate between, say, 85% of the population who might find it difficult to meet the cost of modern medicine and the 15% who might afford to do so. Just before the National Health Service was introduced the Chairman of Council publicly[2] announced that the desire of the profession was to make the service a "resounding success." This must still be its desire. So far as it is possible to judge, the public at large welcomes what limited benefits the Service brings to it—principally, perhaps, the benefit of not having to pay directly for medical aid at the time of receiving it. And the public has run riot in the chemist's shop—at what a cost it is only just beginning to discover. The shocking waste of public money over the inessentials of medicine has left little over for what is more urgently needed. Some important drugs are in short supply, not because they are not being produced in adequate quantity but because they cost dollars. Registrars are being sacked because there is not enough money to pay their salaries and, what is more important, not enough to finance the promised expansion of the consultant service.

The people of this country must face the fact that the National Health Service is heading for bankruptcy. Dr. Ffrangcon Roberts[3] foresaw this as far back as February, 1949, when, observing that "through ignorance and miscalculation in its preparation the cost of the Health Service has been grossly underestimated," he prophesied that the alternative to financial ruin would be shortage of personnel and materials. One way in which a sense of realism and responsibility can be induced is the suggestion made in the *Economist* that charges should be made throughout the whole of the Service, charges which will not prohibit the seeking of advice when it is needed. For example, if each person occupying a hospital bed were to pay as little as 5s. a week for board and lodging the total for the country would be considerable; and so would be the total if everyone were to pay, say, 2s. towards the cost of each *x*-ray film and each pair of spectacles. No medical man wants to place a financial barrier between a person and the treatment he or she needs. And no medical man, either, wants to see a financial barrier between a patient and the food he needs. There is no reason why the State should pay the whole cost of the one or the other.

We cannot escape the conclusion that the failure of the Minister of Health to provide a fully comprehensive health service, and to fulfil his obligations to the medical profession, lies in the economic mess that has come from appearing to promise the people of this country something for nothing. It is difficult to see how the National Health Service can be put on a sound footing and the full resources of modern medicine be at the disposal of the public without considerable readjustment of its economy. The medical profession is discontented and disillusioned, not because of payment, or lack of it, for this or that, but because it sees postponed indefinitely the opportunities for improving the medical care of the people.

MEASURING IMPROVEMENT IN RHEUMATOID ARTHRITIS

It is right that, as medical knowledge widens, the attitude to each progressive stride should become more critical. The science of analysis and determination must keep pace with the scientific experiment, and claims of successful treatment must be upheld by means of standardized methods of assessment. The more remarkable the claim the more searching are the analyses and tests needed to convince other physicians. Knowing this, Hench, Kendall, Slocumb, and Polley[1] took immense pains to check their original work with cortisone and A.C.T.H. in rheumatoid arthritis. Other drugs were substituted at times unknown both to clinician and patient, and various functional tests were used to assess objective improvement. This lead has been followed by rheumatologists in this country, and the tests for objective assessment have been elaborated because of the added necessity to obtain definite evidence of response while supplies of the new hormones remain meagre. These tests can therefore now be used in trying other substances which might theoretically have a cortisone-like action.

An example of this kind of work is the report from Dr. O. Janus, of the Manchester Rheumatism Research Centre, published in this issue. His careful study includes details of the method of testing joint tenderness, grip, and blood flow in knee-joints; and these, combined with the eosinophil response, have enabled him to demonstrate the effects of a single dose of 25 mg. of A.C.T.H. Because many more substances will have to be tried and the potencies of different preparations of

[1] *Proc. Mayo Clin.*, 1949, **24**, 181.
[2] *British Medical Journal*, 1950, **2**, 810.
[3] Ibid., 1950, **2**, 849.
[4] *J. Amer. med. Ass.*, 1950, **114**, 365.

A.C.T.H. assessed, this method of testing with a minimal amount of hormone is a very practical contribution. In a recent paper in this *Journal* Quin, Mason, and Knowelden[2] showed that, although subjective improvement was obtained after injections of saline in two-thirds of a series of cases of active rheumatoid arthritis, the degree of objective change measured by such tests as those described by Janus was relatively slight. Copeman and his colleagues,[3] using a small supply of cortisone for a 10-day course of treatment on five patients, confirmed the value of similar methods of assessment and showed that with cortisone the objective improvement was as remarkable as the subjective (results were compared with those obtained after injection of inert material). There is another aspect of the value of the tests which Janus describes. In order to avoid overdosage in the prolonged treatment which is frequently necessary in rheumatoid arthritis, it is important to discover the smallest amount of cortisone or A.C.T.H. which will keep the patient symptom free. Boland and Headley[4] have shown that between 32 and 65 mg. of cortisone acetate was required to control symptoms for long periods in 36 out of 42 patients. On that level side-effects occurred in only 8.3% of the patients, compared with an incidence of 33% in those on 100 mg. per day. After the initial response to high dosage there follows a difficult period of reduction to a maintenance level, for the patient, fearful of a relapse, will be unable to give an accurate assessment of his own condition. The physician, in determining whether improvement is being maintained, will find these objective measurements of the greatest help.

Owing to the scarcity and the consequent high cost of cortisone and A.C.T.H., and the difficulty of importing them into this country, there is naturally a widespread search going on for other substances with a similar effect. In trying some of these, physicians who have discarded carefully controlled methods of assessment and ignored the natural history of rheumatoid arthritis have been misled into believing that a cortisone-like response can be obtained with a number of substances which have later proved disappointing in other hands. Inconsistencies are to be expected, for in her lucid and excellent summary of what is known about the regulation of cortical-hormone secretion (see page 1242) Dr. Marthe Vogt points to certain wide gaps in knowledge and shows how this uncertainty may affect the results of clinical studies. Nevertheless Hench and his colleagues have shown that the scientific method of investigation is as applicable in rheumatoid arthritis as in any other branch of medicine. Contributions now beginning to appear from British rheumatism centres are adding strength to the foundations of this important research.

PAYING THE DOCTOR

In a recent newsletter the Medical Practitioners Union (M.P.U.) puts forward a scheme of its own for increasing the remuneration of general practitioners and altering its distribution. The M.P.U. Newsletter is written simply and without ambiguity and is attractively presented; so attractively, indeed, that one has the impression after reading it that the matter is as good as settled. It starts off with the fair assumption that "we need more money and a new scheme for its fair distribution." It claims that its proposals lead to the abolition of the basic salary, and it advocates a capitation fee which is uniform throughout Britain. It states that as more general practitioners are entering the Service each year than are retiring or dying more money should be put into the central pool in proportion to the increased number of doctors. If the Spens recommendations are to be carried out this would seem to be essential. Under the heading "What a good scheme must do" the M.P.U. lays down eight points that are at least easy to understand. It wants to make it simpler for the new entrant to establish himself in practice and looks upon a list of 2,500 to 3,000 as a size compatible with good work. It makes what seems on the face of it a sound suggestion—namely, that the capitation rate should be uniform throughout the country.

The M.P.U. introduces what it calls the "expense factor" as a method of making it possible for someone to enter practice without undue hardship. Anyone entering practice will, under the M.P.U. scheme, receive £600 a year as an expense factor for a list up to 1,000. For a list up to 2,000 the figure becomes £700, and £800 up to 3,000. The M.P.U. points out that £300 a year is quite inadequate as a basic salary. Although the M.P.U. calls its fixed annual sum an expense factor, it is nevertheless the old basic salary, but made to look more attractive by an increase in size. Not only that, but the M.P.U. is proposing that this basic salary (or expense factor) should be made universal throughout the Service. It is not possible to say how general practitioners would view such a proposal now, but certainly three years ago it regarded a universal basic salary, though small, as the first step towards a full salaried service. The increase in the basic salary (called expense factor) now recommended by the M.P.U. would, it could be argued, amount to a second step towards a full salaried service. And, indeed, when this is linked to a proposal that encourages a further limitation in the size of the list, the full salaried service seems less remote than it used to be. While it may be argued as a general rule that a large list may lead to hurried and superficial work, there are other factors to be considered. First of all, one man can think and act much more quickly than another and so get through more work; or, to put it another way, one man may be much slower than another in making up his mind about a case. Secondly, the point will come where further restriction in the size of the list will seriously interfere with the freedom of the patient to choose his or her doctor. Lastly, it will never be possible to divide equally the number of general practitioners into the total number of the population so that each practitioner should have, say, only 2,200 patients on his list. Nevertheless the M.P.U. scheme does have the merit of what the B.M.A. has proposed in relation

to an increase in the pool—namely, that there should be some loading of payment for those with small lists. This in itself would tend to discourage an undue preoccupation with the counting of heads.

The M.P.U. will, we believe, be criticized for its suggestion that there should be extra remuneration for years of service. If a man happens to be a bad or an unsuccessful practitioner, a reward of £20 a year after 10 years of service would not necessarily seem to be a fitting recognition of this fact, and when we couple this with the M.P.U. suggestion that there should be no awards for higher qualifications or special skills we see once again the deadly and inequitable hand of the equalitarian who sees virtue only in numbers and turns away from any idea that quality should have its reward. The fundamental weakness of the M.P.U.'s scheme is that it is not related to the Spens recommendations: to desert the Spens Report is to sail on uncharted seas. It will be interesting to see what the reaction will be of those who have received the M.P.U. booklet and have answered its questionary.

RUTHERFORD MEMORIAL

The 13 years which have elapsed since the death of Lord Rutherford in 1937 have seen the development from nuclear physics of a new branch of applied science which has had a great impact on both medicine and biology, and must have a continuing impact through future generations. Professor P. I. Dee, of Glasgow, has quoted the tribute paid by Niels Bohr to "the one who not only discovered the nucleus of the atom but who revealed the transformations which it can undergo, and finally guided the researches which made it possible to effect those transformations." Dee pointed out that to a gathering of physicists drawn from all parts of the world Bohr had found it unnecessary in his tribute even to mention Rutherford by name. His stature has become greater rather than less with the passage of time, and there is a certain advantage that through the accident of the war and its aftermath the Royal Society should have postponed the launching of its memorial appeal until the Anniversary Meeting of the Society during the present week, for the occasion is now of a wider interest.

Through the operation of atomic piles the production of artificial radio-isotopes has become possible on a scale which could not before have been imagined, and their uses in research on metabolism and the mode of action of drugs and hormones stretch out in an apparently unlimited vista, and with no further reservation than that reasonable caution will be needed in both use and interpretation. On the treatment side artificial radio-isotopes, like radium and *x* rays, offer a means for applying high-energy radiation to the tissues, and there is an expectation, so far fulfilled only to a relatively slight extent, that they will add to the flexibility of the methods available. Finally, there is the problem of radiation damage, which, like cancer, has served to focus interest on the cell, and particularly on genetic changes. A greater understanding of these changes may be not the least of the long-term benefits from the incursion of nuclear physics into biology. In each of these three directions the effects of Rutherford's work can be more clearly seen than in 1937, and the memorial which is proposed to him should be the more widely based on that account. The scheme proposes the establishment of Rutherford Scholarships, tenable for three years by postgraduate students within the British Commonwealth for "research in the natural sciences with a preference for nuclear physics." It was as an 1851 Scholar that Rutherford himself came from New Zealand to England, and Rutherford Scholarships are to be held normally in a different part of the Commonwealth from the country of graduation. Secondly, there is to be a Rutherford Memorial Lecture, to be delivered at selected university centres in the British Commonwealth overseas, of which at least one in three will be given in New Zealand, where he was born and graduated. For these two main purposes an endowment of not less than £100,000 is considered necessary, towards which the sum of £30,000 is already available. The co-operation of each of the Dominions and of India has been secured; and, in the words of Sir Robert Robinson, as President of the Royal Society, "it is unthinkable that the appeal should fail."

DURHAM AND THE DOCTORS

The Durham County Council on Tuesday of this week reaffirmed, by a vote of 77 to 13, its decision to require of its employees membership of a trade union or appropriate body as a condition of employment. The Durham Council, which is, we believe, predominantly Labour in sympathy, thus ignores the expressed wish of the Minister of Health, the wishes of its employees, and the expressed policy of two of the principal bodies concerned—namely, the British Medical Association and the National Union of Teachers. We understand that not one of the 53 medical men and women concerned complied with the request of the Durham County Council by November 22, which was the last date for receipt of evidence of union membership. The policy of the British Medical Association remains unchanged, and the Durham medical officers will be encouraged and helped to withstand this local example of petty tyranny. There can be no doubt that, if the medical officers employed by the Durham County Council stand firm, they will eventually win the day. The B.M.A. and the British Medical Guild have both organizational and financial resources to give their colleagues in Durham firm and resolute support. The duty of the Durham County Council is to see that its citizens are properly supplied with those indispensable medical services that are made available through their medical officers. If the county council wishes to sabotage its medical service by imposing a condition of employment which has nothing whatsoever to do with the ability of its medical personnel to carry out their duties properly, then we may hope that the people who elect Durham's councillors will restore to them that common sense of public management which is supposed to be a British characteristic.

TREATMENT OF THE MALADJUSTED CHILD

Much public interest has been shown in the forthcoming inquiry, called by the Minister of Education, into the treatment of maladjusted children in so far as they come "within the educational system." The need for treatment is an important one, and the problem is harder to

define than it is in other varieties of handicap. Yet in the years 5–15, during which the child is largely in the care of the education authority, most of the behaviour problems which show themselves can be treated; and during the same period, without treatment, they can also become permanently established. In the latter event the child is doubly damaged, for not only is the valuable opportunity lost to help him during his formative years but his education as such will suffer as a result of his maladjustment. In spite of overcrowded classrooms and hurriedly trained teachers, it is not generally true to say that schools dislike the maladjusted child, though his nuisance value is high. Nearly always, however, maladjusted children tend to dislike school, where their poor performance singles them out for unwelcome attention. There are many anomalous situations which will fall to be considered by this committee. Are the child-guidance clinics of the local education authority to remain outside the N.H.S.? Some are adopted; others are not—with resulting differences of salary. Are the clinics to be staffed by educational psychologists, and if so should they confine their activities to educational problems? If they attempt to do this, who is to select the cases and what, if any, place does psychotherapy claim? Are these clinics foundering under an overwhelming load, with unmanageable waiting-lists, and, if so, what is to be done about it now that an economy drive is in full swing? Much of this work links with home care, or the lack of it, and with the problems of the broken home and parents out at work. How closely can the educational system be expected to work with parents? Shall the schools take over more, or less, of the parental function? These and many other questions will need to be met and answered. A committee of inquiry enables problems to be pooled and responsibility for solution shared. Public opinion did much to reinforce the inquiry undertaken by the Curtis Committee, and it is to be hoped that parents in general will continue to show their interest and thus help to make the work of the new committee a success.

HIGHER PAY IN ARMED FORCES

Increases in pay for medical officers in the armed Forces, which are to be retrospective to September 1, have been announced and are published in the *Supplement* at page 228. No doubt they will be received with mixed feelings—of pleasure that they have at last been made and disappointment that they are not larger. The Armed Forces Committee of the B.M.A. during the last two years has closely examined rates of pay throughout the medical branches of the Services, and has spent much time negotiating its proposals for bringing them into line with the remuneration that may be expected in the National Health Service. Though events have overtaken these negotiations, which were delayed not through any fault of the committee, the careful analysis that the committee made forms a useful comparison against which to judge the new rates.

The armed Forces have for some time found great difficulty in recruiting enough regular medical officers. Indeed, the establishments are well below strength, particularly of specialists. To remedy this the Armed Forces Committee proposed rates of pay that, so far as some incalculable factors allowed, would make the Services as financially attractive as the National Health Service to young doctors with the choice of their career before them. The Government on the other hand seems to have taken for its standard of comparison not the attractions of civil life but the new rewards obtainable in other branches of Service life. The main problem, therefore, of inducing doctors to make their career in the Services—in so far as it is a financial problem—is likely to remain unsolved. The Government may argue that it has done justice within the sphere of the armed Forces, but it seems to have limited its vision to equity rather than considered Service needs.

The increases for general duty officers are considerably lower than the B.M.A.'s proposals, especially in the middle ranks, where the Association considered that improvement was most needed. They represent in an average career a lead of about 8 to 10% over corresponding civilian remuneration. But the B.M.A.'s statement on these increases concludes: "It is probably fair to state that the new remuneration of general duty officers is not unreasonable in comparison with civilian life." It is the new rates for specialists that are most obviously inadequate. They are unlikely to attract any more to ranks already so depleted that the desperate measure of advertising for civilians at preferential rates of pay has been resorted to in the past. A second-rate, understaffed, and dissatisfied service may well be created if the pay is not reconsidered. At present the scales roughly correspond to those of senior hospital medical officers in the National Health Service. In other words this is an attempt to get specialists on the cheap. The Government may be relying on its aptly timed tocsin to registrars to frighten some of then into joining the Services, there to become specialists. But economic pressure of this kind is shoddy administration, and, by its injustice, will create more unrest and resentment.

National Service medical officers will receive the increased rates of pay only in their last six months of service, and they will not receive the full rate of marriage allowance. This decision, made in spite of the representations of the Armed Forces Committee, is likely only to increase the Government's difficulty in staffing the medical branches of the Services. These men already fill many gaps left by the absence of regular officers. In future an increasing number of them will be tempted to do their National Service before they start their medical training and thus avoid being called up as medical officers.

TEETHING TROUBLES

A simple question and answer in "Any Questions?" (October 28, p. 1013) has provoked some criticism, including a letter which is published on another page of this issue. It is easy to take the extreme view that teething produces nothing but teeth, and against the quotations from Finkelstein and Fischl quoted by our correspondent may be set one from Still[1]: "I would protest against the tendency nowadays to assume that because dentition is a physiological process therefore it is incapable of causing disturbance of health." The question which was posed read as follows, "Can any infant ailments, beyond local

[1] *Common Disorders and Diseases of Childhood*, 1927, London.

reaction, be justly ascribed to teething?" The answer stated that since the cutting of teeth appeared to be painful it led to restlessness and sleeplessness. It went on to suggest that in the child predisposed—for example, by rickets or by virtue of being an epileptic—convulsions might occur. The evidence for this is clinical observation, and Still describes the baby with occasional twitching associated with swollen gums which ceases when the tooth has come through. It is of course likely that with the virtual disappearance of rickets and a higher standard of child care this phenomenon is no longer seen by the present generation of paediatricians, but it seems difficult to dismiss the observations of such a great observer as Still.

The answer then went on to discuss what might happen when teething caused a stomatitis. It is, of course, arguable that such inflammation of the mouth is not directly the result of the dentition but due to the child pushing infected articles into the mouth in an effort to reduce the pain. Even if indirect, however, the clinical fact remains that a number of babies have what appears to be some infection of the mouth and gums during the cutting of a tooth. From such local inflammation, again perhaps more frequently in the debilitated child, local spread to the respiratory tract may occur—pharyngitis, otitis, bronchitis, and even pneumonia were mentioned in the answer, and critics have doubted this. They have also doubted the occurrence of diarrhoea and vomiting due presumably to parenteral causes. Still again is an authority for at least "bronchial catarrh" and "slight looseness of the bowels." He admits with characteristic modesty that the causal relation of dentition to various disorders rests "upon no more solid basis than the observation of many cases." For those who still persist in denying that teething can cause any symptoms of disturbance Still has a final word to say when he mentions the occasional pain and fever associated with cutting of the third wisdom tooth. With this as with the majority of healthy babies, however, disturbances are minimal, and it would be agreed that the "diagnosis" of teething is dangerous if made by the unqualified and not without its perils when made by doctors. It is too sweeping surely to go on to deny the relationship between dentition and certain upsets, rare although such disturbances may be to-day. Critics of our expert's answer might with advantage re-read Still's essay of eight pages on "Disorders associated with Dentition" in the first chapter of his book already quoted.

PROTEINS AND THE CLINICIAN

It is hardly surprising that the progress of protein biochemistry should immensely influence the progress of medicine. Not only are many hormones and many bacterial toxins protein in nature, but the protoplasm of every cell of every tissue is basically an assemblage of protein molecules of various kinds. Myosin, the fundamental contractile stuff of muscle, keratin of skin and nails and hair, all the enzymes of metabolism, haemoglobin and the albumin and globulin of blood—all are protein, all are the study of the protein chemist in his back room, and on his results depend the preparation of toxoids, the understanding of immunity, the treatment of burns, anaemia, oedema, and shock, and of metabolic disorders such as diabetes.

Elsewhere in this issue Professor E. C. Dodds discusses some aspects of the chemist's work, the possibility that he may find a simple, easily synthesized peptide to use in place of the scarce A.C.T.H., and the continued struggle to discover the secret of insulin, which because it is such a stable, easily handled protein has been the most studied of all. There are useful by-products of this kind of research even when the main goal is not attained. "Synthalin" (decamethylene diguanidine) was an early attempt at a synthetic substitute for insulin which proved unsuitable for treating diabetes but fathered a whole range of diamidines valuable for kala-azar and trypanosomiasis.[1] One strand in the development of British anti-lewisite was the study of the way arsenic is bound to sulphur in the keratin of hair.

It is perhaps in the handling of blood, however, that the chemist has so far had his greatest triumph from the clinician's point of view. The large-scale manufacture of dried plasma[2] and its fractionation[3] have yielded serum albumin for use in shock, γ-globulin which contains antibodies for passive immunization against measles and infective hepatitis, purified anti-haemophilic globulin, and concentrated Rh typing sera. The separation of fibrinogen and prothrombin from plasma has made available fibrin foam and film for various surgical uses: haemostasis, repair of the dura mater, dressing of burns and superficial wounds, removal of small renal calculi, etc. All this is based on laboratory work by protein chemists. The possibility of using animal blood for human transfusions, as yet not satisfactorily realized, is nothing more nor less than a problem of protein chemistry.

Knowledge of protein chemistry enters, or ought to enter but is all too often ignored, in another field of medicine—clinical pathology. Not only is the plasma protein level routinely measured but also the erythrocyte sedimentation rate (which depends on the state of the plasma proteins), and blood tests for cancer[4] or other diseases are often devised by clinicians. Many of the investigations of this kind would never be attempted, or would be planned differently, if their authors were more aware of modern physico-chemical knowledge of plasma proteins.[5,6] The plasma contains a complex of many proteins, all sensitive to small changes of salt concentration, *p*H, and the actions of many reagents (including traces of soap). The clinician and the clinical pathologist have drifted too far from the biochemist in this field of knowledge. It is a gap which needs bridging.

We record with regret the death in Belfast on November 26 of Sir William W. D. Thomson, professor of medicine at Queen's University, Belfast. He was 65 years of age. An obituary notice will be published in next week's *Journal*.

[1] Yorke, W. (1944). *Brit. Med. Bull.*, **2**, 60.
[2] Cohn, E. J. (1945). *Science*, **101**, 51.
[3] Janeway, C. A. (1949). *Adv. Int. Med.*, **3**, 295.
[4] Annotation (1950). *British Medical Journal*, **2**, 1213.
[5] Schmidt, C. L. A. (1944). *Chemistry of the Amino-acids and Proteins*, 2nd ed., Springfield.
[6] *Advances in Protein Chemistry* (annually). Interscience, N.Y.

REFRESHER COURSE FOR GENERAL PRACTITIONERS

MENSTRUAL DISORDERS AND THE MENOPAUSE

II. MANAGEMENT AND TREATMENT

BY

P. M. F. BISHOP, D.M.

Endocrinologist, Guy's Hospital and Chelsea Hospital for Women; Senior Lecturer in Endocrinology, Department of Obstetrics and Gynaecology, Postgraduate Medical School of London

Treatment of Menstrual Disorders

Induction of Ovulation

We have already seen that ovulation probably depends on achieving a certain ratio between the waning level of follicle-stimulating hormone and the rising level of luteinizing hormone. Moreover, in individual cases other essential conditions, such as responsiveness of the ovary to gonadotrophic stimuli, may also be absent. It is true that very large doses of chorionic gonadotrophin, such as 10,000 to 20,000 i.u. daily, will prolong the life of a normally established corpus luteum. True pituitary gonadotrophins, not yet marketed, have also been shown in isolated experiments to bring about changes in the human ovary. Nevertheless, no gonadotrophic extract at present generally available has been convincingly shown to induce ovulation in women suffering from non-ovulatory menstrual disorders.

Failure to ovulate and the consequent menstrual disturbance are often symptoms of some general metabolic, nutritional, or psychological disorder, and the ovarian failure will right itself only when the patient's normal health is restored The empirical use of thyroid extract may be justified in such cases. Failure to ovulate *per se*, however, is serious only when it is the cause of infertility, and it is only in this connexion that attempts to induce ovulation seem worth while. Crude attempts to imitate the secretions of the ovarian cycle are sometimes successful in inducing one or two ovulatory cycles, perhaps by conditioning the pituitary in some way to restore normal gonadotrophic activity temporarily. Three courses of stilboestrol (0.5 mg. daily for 21 days) and ethisterone (30 mg. daily from the 14th to the 21st day) with a week's interval between each course, during which bleeding should take place, may occasionally be followed by one or possibly two spontaneous ovulatory cycles —as judged by the temperature records— even in patients suffering from non-ovulatory amenorrhoea. If the patient and her husband have been carefully coached in the interpretation of the temperature records and told to have intercourse immediately the temperature rises from the pre-ovulatory level, there is a chance, theoretically at any rate, of conception occurring.

Oestrogen Haemostasis

It was postulated in Part I of this paper (*Journal*, November 25, page 1214) that uterine bleeding can be arrested if the effective concentration of oestrogen is either lowered beneath or raised above the "bleeding threshold." Progestogen "neutralizes" the effect of oestrogen on the endometrium, and androgen probably acts as an anti-oestrogen. These two hormones, therefore, will lower the effective concentration of oestrogen, though it may be some days before the bleeding stops, and in many instances the treatment is ineffective. To raise the oestrogen level above the threshold is a more rapid and certain way of bringing about haemostasis, and bleeding may abate or cease within a few hours to a day. Oestrogen should be given repeatedly and in high concentration to achieve this object, and toxic side-effects must be expected. It is therefore probably better to avoid using stilboestrol.

Not only is ethinyl oestradiol less likely to produce vomiting but it is the most potent orally active oestrogen available: 0.15 mg. should be given every two hours. If sickness occurs it may be worth while substituting 5 mg. of the conjugated equine oestrogens preparation (distributed in this country by John Wyeth and Brother, Ltd., under the trade name "strogene"), though in these high concentrations toxic effects may accompany the administration of even this "natural" oestrogen and make it necessary to resort to injections of oestradiol benzoate, 100,000 i.u. every four to six hours. This is, of course, "heroic" treatment, and it should be reserved for desperate cases, in which, as the result of prolonged flooding, the patient is becoming exsanguinated and the relatives distracted. An oestrogen withdrawal bleeding may take place two or three days after the treatment, but it is usually moderate in amount and should cause no trouble.

Progestogen Withdrawal Bleeding ("Medical Curettage")

The nature of the bleeding after withdrawal of progestogen with its complete shedding of the endometrium has already been discussed. If the endometrium has been previously primed with endogenous oestrogen, adequate quantities of progesterone will usually induce a "medical curettage." It is possible, therefore, to forestall an episode of metropathic flooding, which generally begins only after some weeks of amenorrhoea, by producing a progestogen withdrawal bleeding at a relatively early stage of this non-bleeding phase. The metropathic flooding can in fact be repeatedly forestalled by performing these medical curettages regularly at four-weekly intervals using injections of 25 mg. of progesterone (dissolved in 1 ml. of oil) on alternate days for four doses (see Fig. 3), or by giving 30 mg. of ethisterone daily by mouth for a week.

FIG. 3.—Prevention of metropathic flooding by rhythmical induction of medical curettage by progesterone.

By the use of oestrogen haemostasis and medical curettage the bleeding of a metropathic phase can be arrested and the next one prevented by superimposing a regular, though artificial, "normal" bleeding pattern on the unpredictable, irregular, and sometimes incapacitating metropathic pattern. One is not, however, attacking the cause of the metropathia, which is failure to ovulate. Nevertheless, this type of menstrual disorder is prone to undergo spontaneous remission. This is especially true in adolescent

girls who have their menstrual and reproductive life before them, and in whom a hysterectomy is therefore unthinkable. It is less true of women in the pre-menopausal age, when failing ovarian function is physiologically progressive until the menopause finally supervenes. At this age, hysterectomy or the induction of a radium menopause are reasonable alternatives to irksome endocrine therapy, especially if this does not go entirely according to plan.

Between these two extreme age groups there is the woman in her thirties. If she is anxious to start a family or to have more children it is obviously desirable to persist with conservative treatment in the hope of a spontaneous remission occurring (for, of course, she will not become pregnant so long as the non-ovulatory pattern lasts). If, however, she has made her family or is a spinster the fact that she is under 40, or any other arbitrarily chosen age, should not be the deciding factor in refusing her a hysterectomy if endocrine therapy fails, or is irksome, or requires to be indefinitely continued. The social, domestic, and wage-earning factors should decide the choice of treatment, and it should be emphasized that endocrine therapy does not cure, but merely prevents, the manifestations of the condition.

If it is eventually decided to embark on hysterectomy the following considerations should be borne in mind: (*a*) one-quarter of the patients will develop menopausal symptoms within two years of the operation if there is no operative interference with the ovaries. (*b*) If some ovarian tissue is resected one-half of the patients, and (*c*) if all ovarian tissue is removed all the patients, will develop menopausal symptoms which in the case of bilateral ovariectomy may be severe, indefinitely prolonged, and not easily controlled. (*d*) One-third of the patients, even if there is no operative interference with the ovaries, will suffer noticeable loss of libido after the operation. Despite this, in over 300 patients who had undergone hysterectomy and were subsequently personally interviewed, less than 10% regretted having consented to the operation.

Androgen Treatment of Menorrhagia

It has been shown that menorrhagia is probably associated with relative failure of corpus luteum development and progesterone secretion, and that this prevents adequate "neutralization" of the oestrogenic effect in the second half of the cycle. Bleeding therefore results in incomplete shedding of a poorly developed secretory endometrium and may occur early and be prolonged and excessive. It might seem logical in these cases to supplement the inadequate endogenous progesterone with exogenously administered progestogen. In practice this proves disappointing. Small doses of androgen, however, seem to diminish the amount and duration of bleeding, so that it becomes tolerable in a number of cases. How this comes about is difficult to explain: possibly the results of the disordered balance between oestrogen and progesterone caused by the relative progesterone failure are rendered less conspicuous if androgens, which may antagonize the action of both ovarian hormones, are used. Methyl testosterone, 10 mg. daily by mouth, should be given for two months.

The moderation of the bleeding pattern may persist for some months after the course of androgens is completed. In any case it is important not to give androgens longer than for two months continuously, and at least a month's interval should elapse between successive courses. Even so, undesirable side-effects very occasionally occur, for there are undoubtedly some, though probably very few, women who are abnormally sensitive to the masculinizing effects of androgens. Mild hirsutism, especially of the upper lip, acne, and, very rarely, hoarseness develop. If this occurs androgen therapy should be discontinued immediately. Fortunately these effects are almost always reversible. It has been suggested that side-effects are more likely to occur in brunettes than blondes, and in women who already show a tendency to hirsutism. Though it is, of course, important to dwell at some length on these undesirable side-effects, this should in no way detract from the use of androgens in menorrhagia, which is surprisingly satisfactory.

Inhibition of Ovulation as a Remedy for Dysmenorrhoea

It is generally agreed that progesterone may cause uterine contractions so strong as to lead to temporary ischaemia of the muscle, with pain similar to that experienced in angina or intermittent claudication. Furthermore, it seems certain that dysmenorrhoea—that is, the so-called spasmodic dysmenorrhoea—does not occur in non-ovulatory cycles, and that exogenous administration of progestogen may actually induce or increase the pain. It has been asserted that the effects of endogenous progesterone may be modified by giving oestrogens in the premenstrual phase of the cycle, but these claims have not been substantiated, and the underlying reasoning is not easy to understand. It seems well established, however, that if endogenous progesterone can be prevented from appearing, by inhibiting ovulation, dysmenorrhoea will not accompany the subsequent uterine bleeding. Ovulation is best inhibited by giving oestrogen early in the cycle. Stilboestrol, 3 mg. daily (or its equivalent), beginning on any day up to the fifth day of the cycle and continued for 14 days, will almost always inhibit ovulation and give rise to a scanty, painless oestrogen-withdrawal bleeding within two or three days of the end of the course.

In order to avoid more or less continuous oestrogen administration a subsequent course should not begin for at least a week after the completion of the preceding course. If the dose has not proved to be large enough to be effective the cycle will either be of normal length and the period painful or else the period will be delayed, usually by about a fortnight, and be painful when it takes place. This prolonged cycle is due to the fact that the dose of oestrogen has been sufficient to inhibit the secretion of follicle-stimulating hormone so that the events of the early part of the cycle are held in abeyance until oestrogen administration ceases, when the normal cycle will begin to unfold, culminating in ovulatory and therefore painful bleeding, which is, however, a fortnight late.

It will be seen that considerable care on the part of the doctor and co-operation on the part of the patient are required to achieve successful results. Furthermore, there is little reason to suppose that oestrogen therapy will affect any cycle other than the one during which it is administered, or that it will play any part in the permanent "cure" of the dysmenorrhoea. Nor, on the other hand, is there any likelihood of permanent harm resulting from this form of oestrogen therapy if at least a week's interval is allowed to intervene between successive courses.

At best this method of treatment can be regarded as a fairly efficient way of tiding the patient over until spontaneous remission supervenes, as it often does during the third decade or after childbirth. At worst the method will be considered an irritating and exacting exercise in "timing," which the impatient doctor and the casual patient will soon abandon by mutual, though perhaps tacit, agreement.

It is beyond the scope of this article to deal with the psychogenic element in dysmenorrhoea or with such therapeutic measures as sex hygiene, cervical dilatation, and

pelvic neurectomy. In spite of these other methods of treatment the doctor may find himself anxious on many occasions to give endocrine therapy a trial.

The Menopause

The reason why both patients and doctors hold such different views on the subject of the menopause, the severity of its symptoms, the need for treatment, and the efficacy of various therapeutic measures depends on the following considerations.

Variation in Severity of Climacteric Symptoms in Different Women.—Hot flushes, for instance, occur in 95% of menopausal women, but in some they are mild and unheeded, whereas in others they are drenching, exhausting, and so frequent that the patient is completely incapacitated.

Changing Attitude of Successive Generations of Women Towards the Menopause.—The Victorian stoic resigned herself to the condition as something she just had to put up with: the mid-twentieth century cynic regards it as her right to demand all possible assistance in bearing an unfair burden practically unknown to and hardly ever appreciated by the male sex.

Variation in Attitude of Individual Doctors to Their Menopausal Patients.—Some doctors consider the condition of little consequence; others have little faith in any form of specific therapy; others believe that every woman, however mild or severe her symptoms, can receive benefit from oestrogen therapy.

Variation in Emphasis on Type of Symptom of which the Patient Complains.—"Nervousness," excitability, irritability, and disturbed sleep call for sedatives; depression, loss of confidence, and emotional instability need reassurance and common-sense psychotherapy; whereas hot flushes, sweating, headaches, and giddiness may respond to oestrogen treatment.

The Doctor's Previous Experiences with Oestrogen Therapy.—Those who have found it ineffective will be less inclined to prescribe it again.

It is clear that each case must be assessed individually, and that neither the type of treatment indicated nor the response to be expected will be the same for every case.

First, one must be sure that one is dealing with the menopausal syndrome. It may appear months or even years before the menses cease; on the other hand, it may not develop until months or even years after menstruation has ceased; moreover, it may last for many years; and, finally, the diagnosis does not depend on the patient's age but on the waning function of her ovaries. It is as wrong to regard every symptom that appears during the fifth decade as menopausal as to refuse to recognize that in a woman below the age of 30 hot flushes may be due to ovarian deficiency. The syndrome is made up of a variety of vague and bizarre complaints, such as indefinite aches and pains, numbness and tingling, and formication, though the most characteristic are hot flushes, depression, emotional instability, irritability, insomnia, palpitations, giddiness, lack of concentration, failing memory, headaches, and paraesthesiae.

Treatment of Menopausal Symptoms

(1) *Reassurance and Common-sense Psychotherapy.*—The impact upon the patient of this strange multitude of complaints may upset the poise she has developed in the course of years. She may fear cancer or some chronic and crippling illness which will make her an invalid. She may, on the other hand, recognize that this is the "change" but may have learnt to dread its consequences from the grim accounts she has received from her women friends. She may fear the effect on her husband of her "lost womanhood." She may resent this blunt reminder of her matronly middle age. Her deteriorating memory and lack of concentration; the inconvenience, embarrassment, and loss of sleep caused by her hot flushes; the loss of confidence in herself, which may be aggravated by attacks of giddiness and palpitation; and perhaps the lack of sympathy which she detects in her own family circle, whom she suspects of resenting her increasing irritability, often send her flying to her doctor in search of that understanding which she so misses in her own home. She needs patient, sympathetic reassurance, with a careful analysis and explanation of her symptoms. She needs to be told that she is not suffering from cancer, that there is no fear of insanity, that her irritability and emotional instability are not her fault, and that something can be done to help her to weather this fleeting climacteric storm.

(2) *Sedatives.*—The climacteric is a time when the reaction of the woman to her environment becomes maladjusted. She becomes unduly sensitive to every little noise, and every afferent impulse is recorded in the sensorium with undue emphasis. She becomes "nervous," excitable, easily fatigued, and irritable, and she sleeps badly. All this clearly indicates the need for sedatives, mild enough to enable them to be prescribed more or less continuously. Phenobarbitone is an ideal preparation. In many cases a combination of patient, sympathetic handling, reassurance, and sedatives may be sufficient to overcome the effects of the syndrome, and more specific treatment is not required.

(3) *Oestrogen Therapy.*—It must always be borne in mind that, however strange and varied are its manifestations, the syndrome is primarily due to declining oestrogen secretion, and that not only are some symptoms, such as the hot flushes, directly due to this but that oestrogen therapy may lead to general beneficial effects. It is therefore probable that in most cases the maximal benefit will be derived from a combination of reassurance, sedatives, and oestrogens.

It might seem reasonable to argue that, if one wants to be sure of overcoming the results of oestrogen lack, it will be wise to give large doses of oestrogen. In fact, however, this is not the case, and high-dosage oestrogen therapy is probably responsible for most of the failures of this form of treatment. The woman whose ovaries are failing or who has recently undergone oestrogen deprivation is exceedingly sensitive to exogenous oestrogen and will nearly always react favourably to small doses. For instance, it is practically never necessary to give more than 1 mg. of stilboestrol (or its equivalent) daily, and results can often be obtained with as small a dose as 0.1 mg. daily. A useful dosage scheme is to give 0.1 mg. thrice daily for three weeks: if improvement occurs the optimal dose between 0.1 and 0.3 mg. daily is determined; if there is no improvement the dose is raised to 0.5 mg. daily for another three weeks, and if necessary to 0.75 mg. daily for a further three weeks. Once the optimal daily dose has been found, repeated attempts should be made to lower it so that the patient is "weaned" as soon as possible. In order to assess the results more easily the patient may be instructed to keep a daily record of the number of her hot flushes. Decrease in the number will provide semi-objective evidence of progress.

Initial large doses raise the threshold of response to oestrogens, so that larger and larger doses will be required; even then the patient may "escape" from the oestrogen control and begin to experience hot flushes again.

Side-effects are more likely to occur with large doses than with the minimal effective dose.

(*a*) *Nausea and Vomiting.*—Menopausal women are specially sensitive to oestrogens and therefore particularly liable to exhibit "toxic" effects. For instance, 1 mg. of stilboestrol (or its equivalent) daily will induce nausea in most menopausal women. If the patient shows intolerance, even to minimal effective doses, some other oestrogen should be employed, preferably a natural oestrogen such as "strogene."

(*b*) *Uterine Bleeding.*—Although this is almost certain to take place if large doses are employed, it not infrequently occurs if small doses (even as low as 0.1 mg. of stilboestrol daily) are used continuously for a prolonged period. If this happens, treatment should be discontinued until the bleeding ceases, and then readministered in courses of three weeks with a week's interval between successive courses, during which a withdrawal bleeding may appear.

(*c*) *Other Side-effects.*—Water and salt retention is a feature of intensive oestrogen therapy. It gives rise to increase in weight, often accompanied by a bloated feeling. Pain, tenderness, and swelling of the breasts may also develop during continued oestrogen treatment, especially if unnecessarily large doses are used.

There is no convincing evidence that exogenously administered oestrogens are carcinogenic. Nevertheless, it is obviously undesirable to submit a menopausal woman, who is specially sensitive, to excessive doses of oestrogens for prolonged periods.

Artificial Menopause

Experience has shown that any interference with, or resection of, ovarian tissue increases the likelihood of precipitating the climacteric syndrome, whereas removal of all ovarian tissues renders this practically certain. Furthermore, the severity of the symptoms of the artificial menopause at whatever age it is performed is likely to be considerably greater than that of the natural menopause. Not only are the hot flushes apt to be very frequent but also so severe that the patient is repeatedly drenched in sweat and quite unable to obtain any continued sleep at nights. In addition to this it is not unusual for the symptoms of depression to be especially marked, leading in many cases to severe depressive psychoses and in some instances to involutional melancholia. Every effort should therefore be made by gynaecologists to conserve all possible ovarian tissue, and, if it is decided to abandon the conservative treatment of metropathia, hysterectomy may be preferable to a radium menopause.

THE CHEMOTHERAPY OF CANCER

EXPERIMENTS WITH NEW COMPOUNDS

A lecture on "The Chemotherapy of Cancer" was delivered to the Fine Chemicals Group of the Society of Chemical Industry at the Royal Institution on November 13 by Professor ALEXANDER HADDOW, director of the Chester Beatty Institute, the Royal Cancer Hospital.

The great majority of cases of cancer at present, said Professor Haddow, were treated either by surgery in an attempt to extirpate and remove the tumour cells, or by radiotherapy to destroy the cells *in situ*. Each of these methods had its limitations, and in any case it would clearly be advantageous, particularly as widespread dissemination was an outstanding feature of the disease, if a less local and more general control of malignancy, such as could presumably be brought about by chemical means, were possible.

This had been well recognized from the earliest beginnings of the study of cancer. Ventures in chemotherapy, of a kind, long antedated the modern developments of surgery. Thus at different times in the past there had been applied such agents as belladonna, aconite, mercury, antimony, and arsenic. Many of these chemical applications had a merely caustic action, as, for instance, in the local use of concentrated acids and alkalis and various metals and metalloids. Arsenic had an action which, though not specific, was less indifferent than the others, and the effects of arsenic in the treatment of cancer had been studied more continuously than those of any other agent.

The chemotherapy of cancer was thus of ancient date; interest in it was by no means a recent development. Nevertheless, there had been during the last few years a new burst of activity, arising very largely from a similar increase of interest in more fundamental work in the cancer field as a whole. In fact, more had been accomplished during the last 10 years than in any other period, though the greater part still remained to be achieved.

The Cancer Cell

Cancer, Professor Haddow continued, was perhaps the most difficult of all biological problems. The cancer cell was simply a modification of the normal cell. Conversion to malignancy of the normal cell might possibly be brought about by a subtle and elusive change of enzyme constitution quite unaccompanied by any grosser alterations affecting protein structure. On this account there was little or no protective reaction on the part of the body or host, such as occurred in parasitic infections. The malignant cell also appeared to be highly stable in its properties, as was shown by the manner in which its newly acquired characters were transmitted and maintained quite indefinitely. In many ways the processes of cell division were reminiscent of a self-propagating mechanism varying in the degree of control to which it was subject.

It had been suggested that the new configuration of the properties which distinguished the cancer cell from its predecessor might be expressed in terms of energy level or level of organization. The transition from normal to malignant appeared to be by way of intermediate cell types. Undoubtedly the normal cell was highly controlled in contrast to the cancer cell, in which the process of cell division might be regarded as almost autonomous. Nutritionally the normal cell might be regarded as highly dependent, and the malignant cell much less so, if not possibly in many ways autosynthetic.

The cancer cell was a unique development of a specific cell type in an adaptive response to unfavourable conditions, and this was only one of the inherent difficulties which confronted any attempt at chemotherapy. Chemotherapy was expected to undo what could almost be regarded as a natural process.

Sex Hormones

In face of these difficulties it was perhaps not surprising that such developments in this field as had taken place in recent years had been accomplished without much thought of practical application, mostly as by-products of more important work. This was certainly so in the endocrine control of cancer of the prostate, which was of great importance as the first indication that the autonomy of the cancer cell was not necessarily complete and that it was in fact open to attack by chemotherapy. This development was very largely due to Huggins and his co-workers at the University of Chicago, and followed preliminary studies on normal and hyperplastic prostate glands of dogs. It was very greatly influenced, as Huggins had told him many times, by Huggins's studies at the Lister Institute in London on phosphatase.

In the special case of cancer of the prostate pronounced therapeutic effects were produced by the administration of a natural or synthetic oestrogen, stilboestrol being the synthetic substance most frequently used. In favourable circumstances improvement consisted of a decrease in size of the primary tumour, possibly regression of metastases in bone, improvement in the blood picture, gain in weight, and relief of pain. All these changes were accompanied by an increase in the sense of well-being, and not a few patients, from being confined to bed, became ambulatory and resumed an active life.

This therapy had now been employed for a sufficiently long time to make it clear that, while cancer of the prostate certainly could not be cured by this means, there was equally no doubt that the foci of the disease became quiescent and life was

prolonged. Again, in a small proportion of cancers of the breast treated by oestrogen there was a most dramatic temporary response. In this connexion it had been interesting to learn of recent investigations in which a favourable response of cancer of the breast or of the cervix had been materially increased by an almost continuous administration of large amounts of water-soluble oestrogen intravenously. There was no doubt that if the mechanism could be elucidated it would be of great importance. A further example of chemotherapy acting through alteration of the hormonal environment of the tumour was the administration of the male sex hormone in cancer of the female breast. There was a curious relationship here—namely, that amelioration was more readily brought about by testosterone in cancer of the breast in women before the menopause, while the beneficial effects from oestrogen were relatively more frequent in post-menopausal cases.

Urethane

The lecturer next described investigations with urethane. Among other conditions in which the action of urethane had been tested and unusually gratifying responses had been forthcoming was myelomatosis. The action of urethane was characterized by an extremely high degree of chemical specificity, and investigators had been very much concerned to decipher the biochemical mechanism of its action. One of the various alternatives which might be considered was that the substance might renovate some deficiency in the chemical differentiation of the cell. The already extensive literature on the action of urethane had amply confirmed the original findings, but so far had added little to the vital problem of mechanism. There was no question that when that problem was solved it would again have very great significance for the understanding of malignant growth as a whole.

These investigations had one curious feature, namely, that while the effects of urethane were first of all observed in the plant cell and later in animal material, and while it was the latter findings which justified and led to the study of the action of urethane in cancer in man, the characteristic effects in leukaemia were detected solely as a result of clinical observation. The various leukaemias in the mouse and rat were relatively refractory to the influence of urethane, and the remarkable effect in the human might have eluded discovery if attention had been directed to the animal alone. That illustrated the hazards of such work.

The lecturer next mentioned aminopterin. Here again the clinical effects were not sufficiently lasting, yet the observation of its action was of fundamental interest and one which would certainly play some part in extending the knowledge of the nutritional basis of cell division.

Nitrogen Mustards

Professor Haddow came next to a different group of substances—the so-called nitrogen mustards, the biological effects of which on tissues in an active state of proliferation were recognized. During the war they had been tried in Hodgkin's disease and various malignant conditions, in which they had undoubtedly a limited therapeutic action, and it seemed not unreasonable to expect to improve the therapeutic effect by chemical modifications. During the last four years some 250 variants had been tested at the Royal Cancer Hospital, and a number of compounds had been prepared, some of which had perceptible advantages in reduced toxicity. He mentioned in particular the chloroethyl derivative of β-naphthylamine. Recent reports indicated that substances of this type might represent a slight advance, especially in the treatment of such conditions as chronic lymphatic leukaemia. Part of the advantage related, not to any marked increase in inherent activity, but rather to ease of administration and relative absence of serious toxic effects. These compounds, like x rays, could be responsible for nuclear damage, production of mutations, and other effects hitherto associated with ionizing radiations. The lecturer showed certain of these effects in mice. Quantitative comparison of various biological effects induced chemically and by radiation, both *in vivo* and *in vitro*, showed a correspondence greater than would seem likely on the grounds of chance alone. The comparison was reinforced by the more recent finding that mustards of this type, again like x and gamma radiation, could also under suitable experimental conditions induce both cancer and mutation. This must be regarded as an important contraindication to the use of them in younger subjects still in the reproductive phase.

Finally the lecturer touched on the recent developments concerning the effects of A.C.T.H. and cortisone in lymphosarcoma, chronic lymphatic leukaemia, acute leukaemia, and certain neoplastic disorders. Again it would seem that any therapeutic action here was subject to obvious limitations and accompanied by certain disadvantages and side-effects; but these observations marked a stage towards an eventual understanding of the different means, direct or indirect, by which the growth of the cancer cell could be affected.

Cancer was almost certainly an error of differentiation. There was very little doubt that it was in this field of cell differentiation that the eventual solution of the problem would be found. At the same time, useful progress could be achieved short of this ideal. It was true that what Lord Horder had called the distinction between prolonging life and prolonging the act of dying must be borne in mind, but when the infinite series of modifications which were within the range of chemistry were considered, together with the great resources of endocrinology and immunology as yet quite untapped, the age of miracles did not seem to be past.

THE SIR CHARLES HASTINGS LECTURE

SIR LIONEL WHITBY ON PREVENTION OF DISEASE

The first Sir Charles Hastings Lecture to be given since before the war was delivered in the Great Hall of B.M.A. House on November 22. The lecturer was Sir Lionel Whitby, regius professor of physic at Cambridge, and a former President of the Association, and the chair was taken by Dr. Charles Hill, M.P. Accompanying them on the platform were Lady Whitby, Sir William Douglas, Permanent Secretary to the Ministry of Health, Sir Henry Souttar, and others. The hall was entirely filled.

Sir LIONEL WHITBY, whose subject was "Can Disease be Prevented?", said that it was necessary at the outset to appreciate how great was the scope of preventive medicine and how many diseases could be prevented. There was indeed hardly anything in the world which did not affect health directly or indirectly; hence the ponderous size of the Ministry of Health, which had to do with drains, sewers, housing, and the huge field of industrial and occupational diseases, many of them with picturesque names such as miner's phthisis, wool-sorter's disease, chimneysweep's cancer, and the like. All these were preventable. Nor were such diseases confined to the labouring classes. They all knew of clergyman's sore throat, boxer's ear, and—a disease frequent when he was young—student's elbow.

Ancient Medicine

Medicine had been in existence for some 2,000 years. At different periods its practice had been variously based upon demonology, witchcraft, appeasement of divine wrath, folklore, shrewd observation of effects without any real knowledge of cause, and also upon proved knowledge such as was now claimed. Demonology as a basis of medicine was very ancient. It formed the background of Egyptian medicine. There was a papyrus of 1500 B.C. which contained incantations and spells for driving out the devil. Disease was believed to be due to devil-possession. Was there not some resemblance between that and the modern treatment by suggestion which was given to psychoneurotic patients? Folklore likewise was very old. It included prevention by charms, amulets, and herbs, and was the basis of herbalism as it existed to-day. Some of it was sound, some artistic, some revolting; most of it was sheer charlatanism. But the herbalist for large sections of the public satisfied the instinctive craving for the unusual, the miraculous, the search for elixirs of life and perpetual youth. Many a time when he was in practice in Harley Street he

noticed among patients who came to him for professional advice that they were wearing an iodine locket around their neck, clearly desiring to "back the horse both ways."

This witchcraft type of medicine was quite unacceptable to the scientist, who demanded controlled experiments, but it might be comforting to some and do no harm and give confidence to people who lacked it.

The Jews of the Old Testament had as their general principle of medicine that God alone was healer and dealt out disease and disaster to man as a punishment for sin. Prevention was appeasement by sacrifice and burnt offering. At the same time a shrewd and observant priesthood formulated a logical code of sanitary discipline appropriate to nomadic tribes. Leviticus and Deuteronomy could be regarded as the first textbooks of preventive medicine, and Moses as the first medical officer of health. They contained instructions for dealing with leprosy—the isolation which was necessary, the burning and washing of clothes, the disinfection of houses, and the priest's inspection before the patient was allowed to return to the community. There were instructions concerning the hygiene of childbirth, disinfection after infectious disease, and food inspection. There were also instructions for field hygiene and discipline which could be applied to an army to-day.

From the First to the Twentieth Century A.D.

Preventive medicine in ancient Greece achieved a high standard. Hygienic measures affecting water supplies, drains, and markets were in some ways in advance of what we had to-day. It was worth noting in passing that the fall of Rome was partly attributable to the impact of preventable disease—for example, the introduction of malaria by soldiers returning from Asia Minor. The fall of Rome was followed by the Dark Ages, when medicine in organized form disappeared for more than a thousand years. During this time, in the fourteenth century, there occurred the Black Death—plague in its most virulent form. In London half the population died. This world-wide disaster, which was now preventable, hindered the march of civilization for centuries. Indeed, the impact of disease upon history might be as great as the impact of war.

Even in the seventeenth century it was revealing to visualize, as one could do from Pepys's *Diary* and other sources, the filthy state of this great city. There was no sanitation, and the conditions were ideal for the dissemination of typhoid and other diseases. At that time occurred the great plague of London, which killed one-fifth of the population. In the eighteenth century, though the English nation was drunken and illiterate, there was a wave of philanthropy which resulted in the voluntary hospitals. At the end of that century occurred what was until then the greatest advance in preventive medicine—Edward Jenner's experiment of vaccination against smallpox, a prophetic prelude to what was to come in the nineteenth and twentieth centuries. At that time 25% of women had their beauty disfigured by smallpox, which was now only a medical curiosity in this country. Whether it would remain a curiosity with the decline of vaccination remained to be seen.

In the early part of the nineteenth century the practice of medicine was less empirical, with many relics of mediaeval witchcraft. Physicians were clever at treating symptoms but knew nothing about causes. Then came the bacteriological studies of Pasteur and Koch. Pasteur's work on immunization against anthrax and hydrophobia was followed by Lister's application of Pasteur's principles to surgery. At the close of the century came the discovery of the cause of diphtheria and the most effective way of treating it.

With the twentieth century came legislation designed to safeguard the health of the school child, to provide facilities for maternal and infant welfare, to deal with the problems of tuberculosis, and to ensure the nutrition of the growing generation. Royal Commissions were set up to investigate such diseases as plague and Malta fever. Much of the advance in knowledge had been influenced and accelerated by three wars in the first half of the century. War was abhorrent, but it had one benefit in that it focused attention on medical problems. A thumb-nail sketch of the positive benefits of war would emphasize this aspect.

The Stimulus of War

In the Boer War more men died from typhoid fever and dysentery than from Boer bullets. In the 1914–18 war, despite the vast number of combatants, typhoid was a rare disease, and lockjaw, after the first unhappy year, also became a rarity, though dysentery again took its toll. Cholera was also controlled by means of inoculations. Between the two wars methods of immunization against diphtheria were perfected, so that this once highly mortal disease was now a rarity. In this period also was developed the first chemotherapeutic attack on such diseases as childbed fever, blood poisoning, and pneumonia. In the war of 1939–45 much of what had been learned about vitamins and the balancing of foods found practical application. Typhoid, tetanus, typhus, malaria, diphtheria, yellow fever, cholera, dysentery, and gas gangrene were now controlled. So effective was the attack on sepsis that in the second world war the chance of surviving wounds was 10 times as great as in the first. Sometimes somatic recovery outpaced psychological repair.

Ehrlich with salvarsan began the control of syphilis, which up to then had been estimated to cause as much as one-third of the morbidity of the nation. Venereal disease, especially thanks to the use of penicillin, had now been reduced, save from the moral aspect, to a problem needing nothing more than effective treatment. The sulphonamides had taken much of the sting from pneumonia, the "captain of the men of death," also from spotted fever and from the bacillary dysenteries. Penicillin, an agent which came very close to Ehrlich's dream of a completely non-toxic, active antibacterial agent, was one of the most powerful remedies against commonly mortal infections, including bacterial endocarditis. Research into the antibacterial properties possessed by other moulds had led to the introduction of streptomycin, a definite step in the treatment of the acute forms of tuberculosis, and aureomycin and chloramphenicol, the last two having an effective action even in certain resistant virus diseases. Chemotherapy had also been outstandingly successful in the prophylaxis and treatment of tropical protozoal diseases such as malaria, African sleeping-sickness, dysentery, and kala-azar. With the world supply of quinine largely in the hands of the enemy in the last war, the work on mepacrine and other antimalarial drugs could be said virtually to have won the Burma campaign.

Respiratory Diseases

Tuberculosis was an ever-present problem, always more pronounced during and immediately after a war, when adequate nutrition was sometimes impossible and when housing shortage led to close contact of infected and uninfected. Its prevention was very much a matter of hygiene. Mass radiography, if universally adopted, would promote the segregation of early cases before they became infective. Much was expected of immunization with B.C.G., while streptomycin and modern surgery could do a great deal for those who contracted tuberculosis.

The problem of preventing the common cold or influenza had not been solved, despite intensive research over many years. The reason was that these diseases were caused by ubiquitous viruses to which it was difficult to create any high degree of durable immunity. Immunity to one virus did not confer immunity to many others. A second reason was that the virus invaded the superficial cells of the respiratory tract, which had a poor blood supply and were not therefore freely bathed by the immune bodies which circulated in the blood.

It must be realized how difficult it was to make a really critical and reliable assessment of any method for the prevention and treatment of such a universal condition as the common cold.

"It is quite meaningless for this or that individual to swear by this or that remedy, from hot whisky to some patent nostrum. To test the efficiency of any remedy in the control of a common and highly infectious disease which has a range of symptoms wide in degree and in duration calls for the most carefully planned experiment involving large numbers in order to obtain results which will stand the fierce glare of statistical analysis."

Poliomyelitis was another disease to which intensive research had been directed. Why was it that no ready solution had been

found? This disease, like the common cold, was caused by a virus which again was ubiquitous and was indeed carried by a high proportion of the population. No effective means of immunization against it had yet been devised. Millions who carried the germ never developed the disease; many who developed the disease never developed the paralysis, and the factors which accounted for this relative immunity had never been solved. Once the virus had gained access to the nervous system the damage was done and it was then too late to do anything about either cure or prevention.

More Outstanding Problems

Where, then, did we stand to-day? An impressive number of infective diseases could be prevented and eradicated. Scurvy, rickets, and other vitamin-deficiency diseases now did not occur in civilized countries where the science of nutrition was appreciated. Great progress had been made in overcoming some of the deficiency syndromes which arose from within—diabetes, cretinism from thyroid deficiency, pernicious anaemia, among others. These could not be prevented, but they could be controlled. Prevention was not possible, because the trouble arose from a degeneration or failure in inherent function of living cells. The subject with diabetes or pernicious anaemia had to be maintained in health by a regular daily supply of the missing secretion or factor. The spectacular advances of the first half of this century concerned diseases such as infections which were extraneous to the human body, not those which were inherent to it. To this latter list belonged the degeneration of the arteries and vital organs, arthritic conditions, and cancerous disease. New ideas had been brought to the understanding of rhqumatic and arthritic conditions with the discovery of the remarkable activity of A.C.T.H. and cortisone, but no one was likely to claim that these substances would constitute a complete cure for these disabling conditions.

As to the degeneration of vessels and organs inevitably associated with advancing age, the failing cells might be temporarily assisted by common-sense advice on habits and mode of life, but not by any simple specific remedy.

Cancer "Cures"

Turning to cancer, Sir Lionel Whitby said that here they were dealing with a vital process, a disorder in cell production, affecting cells which had hitherto multiplied in an orderly and physiological manner. It must be realized that any disease which arose from factors concerned with inherent metabolism and vitality of the living cell was not capable of easy conquest. It was well to remember the historical facts he had already described, how man over 2,000 years had experimented in witchcraft, charms, nostrums herbs, decoctions, chemicals, and secret remedies and had not found anything which would restore order to the unbridled disorder which comprised the cancer process. It needed no great mathematician to calculate the likelihood of a discovery of this kind being made by chance. The discovery when it was made would be based upon fundamental knowledge of cause, in the same way as the vast majority of other medical discoveries.

"It is for these reasons that medical men are opposed to the quack, the nature healers, and other extravagant claimants, particularly when their claims are publicized in the lay press rather than submitted freely and frankly to the profession through the cleansing fire of the orthodox medical press. Such people batten upon the public and exploit their generosity with false hopes of cure. Sometimes with pressure from high circles—and it is a curious fact that the higher the circle the more gullible it is—an official inquiry has to be instituted into the merits of such claims. Sometimes the doctors are accused of being jealous of cures which they themselves have not devised. The ideal of the profession is the abolition of illness. It would go to any length to achieve that ideal, even though, paradoxically, it would destroy its own means of livelihood. Such accusations are sheer nonsense. Members of the profession would welcome any cure, but they demand evidence, and they have the interests of the public at heart in opposing such claims until the evidence is produced."

He wished to end on a note of cautious optimism. The onset of cancer was insidious. Its elimination in the individual could frequently be accomplished in the earlier stages, before dissemination, by efficient and radical surgery. In recent years the public had been gradually educated to consult their doctors on the occurrence of any suspicious symptoms. In this field of education, with care to avoid the creation of universal cancer phobia, much more could be accomplished. There were signs, however, that the long years of patient laboratory research into fundamental principles had begun to yield hopeful dividends, if not any radical cure. The synthesis of stilboestrol and the discovery that it would influence and retard the growth of secondary cancerous deposits arising from cancer of the prostate was an important landmark and illuminating pointer for the future. New vistas had been opened up by nuclear physics. A detailed and intricate study of cell metabolism and cell chemistry had been made possible by means of radioactive isotopes. There was a reasonable prospect that the steady accumulation of knowledge on the chemistry of vital processes would lead eventually to a proper understanding of the fundamental cause of cancer.

Could disease be prevented? He hoped that his broad review had answered part of the question. Man was mortal and must eventually die. When this time came to any of them they would desire that the end should be swift and painless. But during the threescore years and ten of the allotted span, could disease be prevented? What could be done to prevent tragedy in youth and within the span of useful life? What could be done to prevent a lingering and painful death? If as much were accomplished during the second half of this century as during the first half then man indeed could take heart.

Sir WILLIAM DOUGLAS proposed a vote of thanks to the lecturer. The lecture, he said, had been true to the Hastings tradition. The whole life and training of the founder of the B.M.A. had been devoted to the cause of public health and preventive medicine. About 100 years ago Hastings was besought by the mayor and corporation of Worcester to take matters in hand when the city was threatened by plague, and his resolute action was long remembered. As for the lecturer of the evening, he had had many opportunities of appreciating Sir Lionel's qualities of mind and character. On official grounds he was glad to have been invited to propose this vote of thanks to him, because it was in the field of preventive medicine that the doctor, the scientist, the administrator, and the legislator could meet together in a not always unfruitful task.

The vote of thanks was enthusiastically accorded.

Reports of Societies

GENERAL PRACTICE SECTION

ROYAL SOCIETY OF MEDICINE INAUGURATION

A General Practice Section—the twenty-sixth on the Society's list of sections—was formally inaugurated at the Royal Society of Medicine on November 22.

Lord WEBB-JOHNSON, president of the Society, in a brief address, said that the new section was generally welcomed by the Fellows and had passed through its initial stages without the slightest difficulty or opposition. One of the values of the new section would be as a means of narrowing the gap between the general practitioner and the specialist. In recent years the gap had certainly widened in some respects, though it had narrowed in others. It had widened in surgery. When he himself started surgical practice as assistant to Sir William Thorburn in Manchester the patients were frequently in local hospitals and nursing-homes and the general practitioner remained in close touch with them. He thought that the surgery in those days was quite good, but in certain fields it had now become so complicated that it was essential for the surgeon to be on his own pitch and with his own team. There were other fields also in which the general practitioner felt that he had lost a certain amount of touch with his specialist colleagues.

In another respect, however, the gap had narrowed. In his own early experience the general practitioner would introduce a complicated case and the surgeon started from zero to work out the diagnosis. Nowadays the general practitioner almost as

a rule came up with a complete dossier, and all the surgeon had to do was to say, "Yes, what about Friday of next week?"

All engaged in the practice of medicine would deplore the present tendency whereby general practitioners were deprived of opportunities which should be theirs at the local hospitals.

Another reason for the new section was to make it easier for the general practitioner or general surgeon to keep in touch with the results of research. The section would also help to keep alive in general practice the principles of academic and scientific medicine which they all learned in hospital but often found easy to forget on going out into practice. The closer the collaboration the greater would be the advantage on all sides. The membership and presence of general practitioners would be a source of strength to the Society as a whole. This should be an educative section, and it should not be a subdivision of any other. It should be a focal point for the correlation of the work of other sections in a practical bedside approach.

General practitioners would be drawn into all the activities of the Society. They would have a meeting-place, opportunities for social intercourse—at which quite possibly they would learn more than in formal meetings—and access to what he believed was the best medical library service in the world. He was well aware how isolated and individualistic many general practitioners, from the very fact of their situation, tended to become. Membership of such a section would be a wholesome corrective. He invited them to take full advantage of the facilities which the Society offered. Those facilities were at present provided under some difficulty, but plans were afoot, and as soon as the word "Go" was uttered active preparations would be made for the full provision of what in effect would be a medical club, with all the opportunity which it gave for exchange of views and mutual understanding.

The SECRETARY (Mr. Geoffrey Edwards) reported that under the by-laws the new section had been fully established. Notices had had to be sent out giving opportunity for objection by Fellows, but no objections had been received. The officers and council had been nominated necessarily in the first instance from among those who had been most active in promoting the section. The list of nominations for 1950–1 was as follows:

President—Dr. G. F. Abercrombie.
Vice-presidents—Dr. W. N. Pickles, Dr. J. D. Simpson.
Hon. Secretaries—Dr. G. O. Barber, Dr. G. M. Kerr.
Members of Council—Drs. R. Cargill, L. V. Gimson, Sir Wilson Jameson, Drs. J. H. Le Brasseur, L. C. Lyon, O. Plowright, Marion Ravell, E. B. Rayner, A. Talbot Rogers, E. P. Scott, and J. D. Wells.
Representative on Library and Editorial Committees—Dr. W. E. Chiesman.

These were unanimously elected.

Dr. ABERCROMBIE then took the chair and expressed his appreciation of the compliment. He appealed to members for papers for future meetings, preferably recording observations made in their practices. He also expressed in the name of his fellow officers and council their indebtedness to Mr. Edwards for the infinite amount of trouble he had taken in the formation of the section.

It was announced that the first scientific meeting would be held on December 20 and that the subject for discussion would be, "What is General Practice?"

A successful British Council Exhibition of nearly 200 textbooks and some 150 periodicals on medicine, engineering, and agriculture, held on the Peruvian–British Cultural Association's premises in Lima in September, resulted in more than 125 orders being placed—a satisfactory figure in view of the relatively high cost of most of the books and the fact that they were not in the buyers' native language. An article by Dr. Paz Soldan in the newspaper *La Cronica* was indicative of the professional interest aroused as well as being a tribute from the author, a leading Peruvian physician who played a major part in arranging for the visit of Dr. Douglas Guthrie, of the University of Edinburgh, some two years ago to lecture on the history of medicine.

Correspondence

Guy Fawkes Day—The Afterglow

SIR,—In previous years we have given warning in the local press of the danger of fireworks, particularly to children. We have stated that young children have no "safety sense," and consequently should not be allowed to hold fireworks, or store them in their trouser pockets. Adults should organize the display, supervise the letting off of fireworks, and see that fireworks are never thrown.

Here is the result of the neglect of these precautions from the experience of one hospital on Guy Fawkes Day, 1950. Sixty casualties were treated by us for injuries from fireworks: 35 were burns, 18 were lacerations due to explosions, and 7 were eye injuries. The circumstances of these injuries were:

29 were caused by fireworks going off in the hand.
11 were caused by fireworks exploding in the face; most of them were thrown.
4 serious burns were caused by fireworks exploding in the trouser pocket because an apparent "dud" was replaced and ignited the store.

The average age of the 49 males was 14 years, the youngest 4 and the oldest 45. There were 11 female patients, average age 13 years—the youngest a baby of 5 months, the eldest 45. We were told that the baby "cried for a firework and was given one"; it exploded, causing severe injury to her hand. Five of our patients suffered extensive full-thickness skin loss burns of the face and body and will have lifelong scars, and two will have some permanent impairment of sight.

That one hospital staff should work through Saturday night and well into the afternoon of Sunday dealing with the immediate treatment of these injuries is unimportant, yet this effort in no way represents the hospital treatment essential to this small group. We have, for example, one patient still under treatment for serious burns received on Guy Fawkes Day, 1949. What is important is the unnecessary suffering, particularly to children, and the cost of treatment to the country as a whole of casualties from this annual celebration. The Guy Fawkes Day casualty list is yet another example, if indeed another is necessary, of the meek acceptance by this generation of the inevitability of accidents. *The Times*, in a recent leader on road safety, stated that "all road users have equal obligations to share in the team-work of avoiding accidents. It is work of urgent national importance, deserving of the highest priority from every citizen." The same may be said of all types of accident. The peacetime accidents rate now stands at over one million each year, a casualty list more bloody than that of most military campaigns in our history, and "shows no signs of disappearing from the grim recurrence of official statistics."—I am, etc.,

Birmingham. WILLIAM GISSANE.

Cost of Academic Clinical Office

SIR,—In former times it was customary for aspirants to the Diplomatic Service to be asked, at their selection interview, particulars of their private means. I am surprised to find that this information is not required of candidates for academic clinical posts. Particulars of my own income and expenses will show how essential this information is to the selection committee burdened with such an appointment. I give them below without the slightest criticism of my university, which is both understanding and generous, but in this respect impotent. These figures are entirely factual and can be proved.

It might be said that some of these expenses are extravagant. I am aware that certain of my whole-time professorial colleagues do not travel by private car. I have no knowledge of their reasons for this, but in my own case I find a completely reliable car absolutely essential for the efficient performance of my work. The entertainment expenses I have included are lower on paper than in fact they are, because I have made no allowance for the domestic staff I require to enable me to entertain people in my home and to invite people

Expenses	£	£
Motor car, capital cost, spread over four years	350	
Petrol	107	
Tax, insurance, garage, repairs	250	
Societies and journals	98	
Travel (three years' average)	160	
Books	100	
Telephone	92	
Rent of bedroom in hospital	50	
Entertainment	250	1,457
Health insurance deductions		50
Superannuation		140
Income-tax deducted at source		900
Total		2,547

from abroad to stay with me. Other items, too, might be questioned, but the expenses I incur are substantially less than those of my part-time colleagues who engage in private consulting practice and are less than my own expenses were before I left private consulting practice for whole-time employment. The only real difference between expenses of part-time and whole-time consulting surgeons, apart from the question of accommodation, is that the expenses of the former are allowed by the income-tax assessor, while the expenses of the latter are not. The tax inspector affords me an overall expenses allowance of £250.

Of my gross income of £2,750 there thus remains to me a net income of £200. Expressed as a weekly wage of £3 7s. 6d., this compares not very unfavourably with the reward of the lowest-paid unskilled labour in this country. My working hours are, however, subject to no restriction other than that imposed by sleep and inanition, and they number 70 or so in the week. The hourly rate for my work is thus a trifle less than one shilling, and less even than the piece-rate of most Asiatic labourers.

This position would of course be untenable were I not, as I imagine most academic clinicians are, endowed with substantial wealth from other sources. This, however, cuts both ways, and rather painfully. Taxed as I am on my gross salary as well as on other income, I pay on that gross salary a few hundred pounds in surtax. The surtax on my salary in fact exceeds substantially my net income from it. I would be financially more comfortable if I resigned my appointment and stayed at home. I enjoy my work sufficiently, however, to regard it as a satisfying and delightful, though extravagantly expensive, hobby.

This melancholy situation could be rectified only by the proper acceptance of my expenses both by my university (which might well be sympathetic) and by the Treasury (which would not). It is comforting to recollect in this connexion the Minister's decree, promulgated some years ago and presumably after full examination of clinical university appointments throughout the country, that special awards (though not of course sessional fees) will be paid in full to university clinicians selected to receive them. This additional income, intended, one would suppose, as a reward for the clinical activities, clinical teaching, and clinical research which should occupy 95% of the academic day, will be heavily taxed, but will to some extent alleviate the present financial disorder of the academic clinician. It may also encourage men without private means to apply for academic clinical vacancies. When a clinical chair remains empty, or is filled by a part-time director (and this has already happened), those of us who have watched the slow and sometimes difficult establishment of whole-time clinical departments in universities feel great regret.

The personal details of my income which I have provided force me to ask your permission to sign myself

ACADEMICUS.

Displaced Registrars

SIR,—Your excellent summary (November 18, p. 1158) of the situation caused by the threatened dismissal of 1,100 registrars can hardly be improved upon, but I feel that no member of the medical profession should miss an opportunity of protesting against an injustice being perpetrated. Here are 1,100 doctors, many of them ex-Service men, whose professional careers have already been once disrupted, who have spent two to five years of a vital phase of their lives in hard studies with the promise of being allowed to continue training as specialists, and who now find themselves to have been "led up the garden path." There can be no argument about the rights and wrongs of the situation; there can be no argument but that justice demands a revocation of the threatened action.

I write, however, to draw attention to the concomitant impairment of medical service which must result when 1,100 partially trained doctors are discarded. In some specialties, for example psychiatry, there always has been a shortage of experienced personnel in relation to the scope of work. It is only by virtue of an influx of enthusiastic trainees that modern psychiatric needs have been met with a greater degree of adequacy. Discarding these men will undoubtedly entail a reduction of psychiatric services for the public. What makes the threatened situation more serious is that the circular R.H.B. (50) 106 does not plan practical measures for the replacement of staff that may be lost. No suggestion at all is made for the loss of middle registrars; and the idea that the already overburdened general practitioner will be able to spare the time (if he has by fortune the experience) to perform the duties of a senior registrar at cut rates does not seem proper or practical.—I am, etc.,

Basingstoke. I. ATKIN.

SIR,—Reduction in the number of senior registrars would appear to be in the best interests of the specialist aspirant. It would ensure that a man who had completed three years in this grade would be likely to get a specialist appointment. The method of introducing this change, however, is unnecessarily harsh and the scheme is too rigid. If it is applied as suggested it will throw out of employment many hundreds of senior registrars at the end of their period of office, men who deserve well since most of them have had considerable war service. We would suggest that the scheme be introduced gradually and that the term of service of these men be lengthened appropriately, so that most of them may be absorbed into the consultant ranks. Naturally the rate of production of new registrars would be slowed down for some time to allow this absorption to take place. A few years should see the whole matter adjusted at the new level. In the meantime, registrarships in excess of the new establishment would be declared supernumerary.

Consultant vacancies do not necessarily occur at regular intervals. This means that a man who has completed his term of service will often have to wait, possibly for as long as a year, and, at the end of that time, contest a vacancy, possibly unsuccessfully. During this waiting period he will have to maintain himself and his family as best he can.

The scheme takes no note of the fact that surgery is fluid and always advancing. Specialties are developing, and men have to be trained in them. In the case of urology, for instance, not enough young men are being trained in that most important procedure, per-urethral resection of the prostate. The plan fixes for all time the number of urological registrars in relation to the number of vacancies due to occur, and ignores the possibility of new appointments. The plain fact is that once again the human factor is being ignored, and an attempt is being made to squeeze a quart-sized problem into an administrative pint pot.—We are, etc.,

Birmingham. H. DONOVAN.
A. GOUREVITCH.

SIR,—The Ministry of Health circular on registrar grades contains many misconceptions, but the overriding one is the notion that the training of a specialist should be complete after five years. This may be so for some individuals in some specialties, but it is my opinion that this is far too short a period for the training of the average consultant. A general practitioner sends a patient to a consultant for an expert opinion, which he expects to be based on sound judgment, and sound judgment can be attained only by long experience. Does anyone seriously suppose that five years of training will make a consultant surgeon? Would any of the Ministry's experts who drew up this scheme submit their own bodies to the surgical judgment of a five-year specialist? I am an

orthopaedic registrar and have had two years of general medicine, two years of general surgery, and three years of orthopaedics. According to the standards of the N.H.S. I should be fully trained in two years, but in my own estimation I require at least another five years before I would feel competent to give a sound judgment on any orthopaedic problem which might be presented to me. In the past specialists had to wait till they were 35 to 40 or longer before they were awarded full consultant status, and yet a specialist can now be completely trained seven years after qualifying, which means that some will complete their training for consultant posts at 30 years of age. Some may indeed be fully trained by then and be prepared to take full charge of a department, but how can any hard and fast rule be made ?

Some may say that the time of training is adequate provided it is done at proper centres. This brings me to my next point. Of what should specialist training consist ? From the allocation of senior registrar appointments, one gathers that the medical schools are to be the main training grounds of specialists. But it is not generally recognized that, while the teaching centres give one a good theoretical and philosophical background, it is at the far more numerous non-teaching hospitals that the most prolific practical experience is available to the young specialist. This is borne out by the fact that in the past the post of junior honorary in teaching hospitals was supplemented by posts held concurrently at non-teaching hospitals where the bulk of experience was gained. We all know how ill-suited for general practice is the academically trained newly qualified doctor. Yet it is proposed to keep this theoretical doctor in the academic aura and train him to be a theoretical specialist.

Perhaps the most surprising feature of this circular is the suggestion that suitably experienced G.P.s should take over the work of displaced registrars on a part-time basis. How does this suggestion square with the fact that specialist G.P.s who were doing this very thing before the N.H.S. have now been almost completely liquidated by the regional boards ? Many G.P. specialists were expelled from hospital service, and those who were accepted for consultant status were obliged to give up their general practice. After relinquishing their practices and dissolving partnerships they are now informed that the specialist G.P. is to be reintroduced into our hospitals.

But what of the assumption that the G.P. would be willing or able to do part-time registrar work ? Has the Minister any idea of the volume and scope of work done by registrars ? If so, I do not think he would be so ready with suggestions for replacing them or declaring them redundant. For my own part I work a full 48-hour week, often longer, I see and treat about 70 orthopaedic and 140 fracture and accident out-patients a week, look after 30 or more orthopaedic and accident beds, and perform many minor and major operations. Owing to the shortage of house-surgeons I am almost perpetually without junior assistance. In addition it should be remembered that when consultants are on holiday or attending meetings, etc., the full work falls on the registrar, because locum consultants are non-existent. Now I do not think I work exceptionally hard and I am not complaining, but I should like to know how jobs such as mine are to be filled by a part-time G.P., unless it be by several G.P.s working in rota. Whether G.P.s with the qualifications and experience could be found I will not discuss, but what I wish to emphasize is the fact that the average registrar in my experience is doing a full-time job of work. He does not, in fact, regard himself primarily as a trainee but as a worker who is incidentally training in the school of experience. The training is continuous and forms part of his work, and there is no arbitrary time limit where his training ends and his real work begins. When the registrar thinks he is ready to shoulder the responsibilities of consultant practice let him be appointed on his merits in competition with others. If he does not succeed why should he not continue to serve as a registrar ?

The idea that senior registrars should all be incubated in prescribed centres and, after a prescribed registrarship period, should all automatically be hatched out as full consultants is not in the best interests of medicine. But it also reveals a lack of appreciation of the fact that, whatever registrars may be in theory, in actual fact they are filling a very important gap. In theory they may be trainees, but in practice they are workers, as the Minister will find to his cost when he dismisses them.—I am, etc.,

Halifax, Yorks A. W. FOWLER.

SIR,—I should like to express my congratulations on your strongly worded leading article (November 18, p. 1158) commenting on the Ministry's decision to terminate the appointments of 1,100 registrars. May I, however, draw your attention to one point of which the full implications appear to have been overlooked ?

Among the measures proposed to bring about the reduction in numbers is the instruction that senior registrars' appointments should be terminated after three years as a matter of course. Now it is obvious that consultant posts will be available to a small proportion only of those senior registrars who are *at present* in their third year of appointment, and hence a goodly number of those to be—to quote your editorial—" put into the discard " will be precisely those most experienced registrars who are held to have completed their training.

In effect, a situation is being created in which youth and inexperience will be virtually the best passports to the higher ranks of the profession.—I am, etc.,

London, W.1. DAVID WEITZMAN.

Abnormalities in Developing Chickens

SIR,—Congenital abnormalities have three main groups of causes, which may act separately or in combination. The first group is genetic, which has been studied more than any other: the second group is mechanical, on which I have done a good deal of work myself: the third group is that of toxic factors, such as *x* rays, rubella, lack of vitamins, or insulin. I have been privileged to see Dr. A. K. Duraiswami's slides and specimens, and to discuss his work on this third group of factors with him (see *Journal*, October 28, p. 1002).

Dr. Duraiswami claims to have demonstrated that:

1. Certain abnormalities whose cause has so far been unknown can be produced by injections of insulin.
2. Different abnormalities can be produced according to the stage of development of the foetus when the injection is given.
3. The severity of the abnormalities is in direct proportion to the amount of insulin administered.
4. The action of the insulin can be countered and its effects aborted by administering certain substances.

Now, if these claims are correct, and they appear to me to have been most carefully checked, it is obvious that this work is of great importance, and may increase considerably both our understanding and our power of treating a very puzzling group of conditions.—I am, etc.,

London. DENIS BROWNE.

Dead Bodies in Water

SIR,—Your correspondent (November 18, p. 1172) will find this question fully discussed in Chapter 6, Book 4, of *Vulgar Errors*, by Sir Thomas Browne, which first appeared in 1646. The author notes the belief that the female body floated face downwards as being first mentioned by Pliny and in his day as " yet currant," but he himself thinks it " an assertion wherein the *hoti* or point it self is dubious: and were it true, the reason alledged for it is of no validity." He ends the matter by writing: " But hereof we cease to discourse, least we undertake to afford a reason of 'The Golden Tooth,' that is, to invent or assign a cause when we remained unsatisfied or unassured of the effect." In any case I would commend this most fascinating of bedside books to your correspondent—but perhaps he knows it already.—I am, etc.,

Halse, near Taunton. W. BALY PEACOCK.

SIR,—I read with considerable interest the letter written by Dr. Eric Gardner (November 18, p. 1172). My own experience on the Thames here is the direct opposite of that of Dr. Gardner. I have never seen a male corpse floating face upwards, either in the Thames in its tidal reaches or, during the war, in the Mediterranean or the Pacific.

In the past 18 months I have seen three male corpses, all face downwards, which are sufficiently recent to be very clear in my mind. The parts above water were the shoulders and rump, the head well bent down, arms hanging downward, and legs in similar position, giving the impression of a bather half-way off the springboard attempting a dive as close to the end of the springboard as possible.

I always understood that a woman floated face upwards owing to the flotation effect of the mammary tissues, etc., but have no personal experience in the recovery of female corpses. It is of interest that I have questioned six local watermen here in the past week, all of whom said, without any hesitation, that "males float face down, and females face up after drowning."

I note that Dr. Gardner writes from Weybridge, and it occurs to me that corpses may behave differently in fresh water as opposed to salt water. Perhaps some of your correspondents can throw further light on this very interesting matter.—I am, etc.,

Hulk "Hygeia," off Gravesend, Kent. HUGH WILLOUGHBY, Deputy M.O.H., Port of London.

Ring Round the Penis

SIR,—The treatment of cases of constricting rings and bands around the penis is usually dismissed in standard textbooks of surgery with the statement that they should be cut, although one book does state that in some cases the services of a blacksmith may have to be used. The following case is of interest because it shows the difficulty that may be experienced in removing such a constriction.

The patient, a married man aged 23, who was an electrical engineer, attended Casualty one evening, having ridden up to the hospital on a bicycle. Around the middle of the shaft of his penis was a circular ring of hardened steel. The ring had a lumen 1 in. (2.5 cm.) in diameter, and the ring was ¼ in. by ¼ in. (1.9 cm.) thick. Attached to one side was an iron rod 14½ in. (35 cm.) in length. The bar was 1¼ lb. (800 g.) in weight, and the patient stated that it was a home-made poker.

There was gross oedema of the penis, which beyond the constriction measured 2½ in. (6.4 cm.) across. The difficulty was to reduce this through the lumen less than half its diameter. The patient was taken to the theatre, anaesthetized with thiopentone, gas, oxygen, and ether, and the penis was bound from the tip down to the constriction with a 1-in. bandage, and left like this for a quarter of an hour. On removal it was found that the oedema had considerably diminished, and it was possible by traction and pulsion slowly to work the ring towards the glans, keeping continual pressure on this to prevent redevelopment of the oedema. Eventually, after 45 minutes' work, the ring was removed, and apart from haematomata no serious damage appeared to have been caused. This was surprising in view of the patient's condition when he presented himself, when the problem seemed insoluble apart from amputation of the penis. If we had failed to reduce the oedema by pressure it was suggested that, after making numerous small incisions in the oedematous part, suspension in a supersaturated solution of NaCl might have reduced the oedema, though whether or not there would have been much tissue damage is not known.

The patient's penis after recovery measured in a flaccid state 7½ in. (19 cm.) in length and 1½ in. (3.8 cm.) in diameter, so it would appear to have been a not inconsiderable feat to have got it through the ring at the start.

We are indebted to Mr. R. E. Gibbins, consulting surgeon, under whose care this case was admitted, for permission to publish it.—We are, etc.,

Kidderminster. M. DRURY. K. MCKENZIE.

Transfusion and Viral Hepatitis

SIR,—Your leading article of November 11, page 1103, contains certain statements which may give a wrong impression.

Although three incidents have recently been reported from the U.S.A. in which hepatitis has followed the use of plasma or serum irradiated with ultra-violet light, it is hardly justifiable to condemn this method of sterilization out of hand, since the conditions under which the plasma or serum was irradiated are not known. The evidence presented by Oliphant,[1] Oliphant and Hollaender,[2] and by Blanchard and his colleagues[3] indicated that irradiation, under the conditions used by them, was effective, at least against a single strain of virus.

The technique of irradiation is complex; for example, slight deviations in the procedure may reduce the time or intensity of irradiation below the critical limits, thus failing to inactivate the infective agent. It is thus clear that the process must be continuously and accurately controlled and be reproducible from batch to batch of plasma before its effectiveness or lack of effectiveness can be conclusively demonstrated. Suitable methods of exercising this control are being developed. It is also clear that detailed follow-up surveys of the recipients of plasma, similar to those already made in this country, must be conducted before conclusions can be drawn regarding the relative merits of different methods of sterilization of plasma. It is to be hoped that the conditions under which the plasma or serum involved in the American cases was irradiated will be reported in the fullest detail, so that fair comparisons may be made between the effects of these and the numerous other batches of plasma which have been irradiated.

While the use of transfusion has increased since the recent war, the absolute amount of plasma used since 1946 has diminished. Simultaneously, the transfusion of whole blood, which previous surveys have shown to be associated with subsequent attacks of hepatitis in relatively far fewer cases, has grown apace, and to-day the ratio of blood to plasma used is about 10 to 1. It is perhaps worth recalling that the survey made by Lehane *et al.*[4] showed that the incidence of hepatitis after 10-bottle pool plasma (the smallest practicable pool) was only slightly greater than that following the use of whole blood (0.8%).—We are, etc.,

Virus Reference Laboratory, Colindale. F. O. MACCALLUM.
Lister Institute, Elstree. W. D'A. MAYCOCK.

REFERENCES

1 *Bull. N.Y. Acad. Med.*, 1944, **20**, 429.
2 *Publ. Hlth Rep., Wash.*, 1946, **61**, 598.
3 *J. Amer. med. Ass.*, 1948, **138**, 341.
4 *British Medical Journal*, 1949, **2**, 572.

Haemolytic Streptococcal Gangrene Treated with Streptomycin

SIR,—After reading the article by Mr. R. Marcus (August 12, p. 394) I wish to add some remarks with reference to an article I published in *N.Z. med. J.* (August, 1949, p. 380). It so happened that I encountered three cases of the condition within a few weeks of each other. Two cases were critically ill, and the literature advocates extensive excision of the wound and zinc peroxide dressings, a drastic procedure, especially for one case with a burst abdomen. All had been on intravenous glucose–saline and had had penicillin and sulphonamides in heavy doses. All presented irregular pyrexia and pulse rate, with associated exhaustion rather than toxaemia.

I was struck by Meleney's work, and felt that, if a drug could be administered capable of destroying one of the organisms in the bacterial symbiosis of *Staph. aureus* and a micro-aerophilic streptococcus, then the disease process might be stayed. As a last effort streptomycin was tried, and the results were nothing short of miraculous. All patients were improved in 24 hours, and in 48 hours clean healthy granulations were seen. All recovered. I append brief notes of the cases.

1. An obese man, aged 57, who eight days after the removal and drainage of a gangrenous perforated appendix and appendix abscess had a burst abdomen sutured. The patient became very drowsy, and gangrene appeared in the wound. He had 6 g. streptomycin in divided doses over 72 hours, with complete recovery and healing of the wound within seven days.

2. An obese female, aged 45, developed gangrene in the area of a transverse colostomy 12 days after a Paul-Mickulicz resection of the transverse and descending colon for a recurrent volvulus of the colon. Complete recovery in 48 hours after the administration of 4 g. streptomycin in divided doses.

3. A female, aged 28, developed post-operative gangrene of the wound 12 days after a subtotal hysterectomy for fibroids, at which operation the appendix was removed (a common procedure in any laparotomy). Cleared in 24 hours after the administration of only 2 g. streptomycin.

All cases were given a total of 6 g. streptomycin each over a period of 72 hours (1 g. 12-hourly).—I am, etc.,

Dunedin, New Zealand. H. M. KARN.

Unabsorbable Sutures

SIR,—There have been two recent accounts (*Journal*, September 16, p. 659, and October 21, p. 949) of unabsorbable sutures being found in the uterus some years following caesarean section. It was suggested in the first that the ligatures, being silk, were therefore unabsorbable and responsible for accompanying sepsis. The use of such sutures was therefore condemned. A very similar case is described below, and again the suture material was apparently thread and was still present in the uterus when removed 13½ years later.

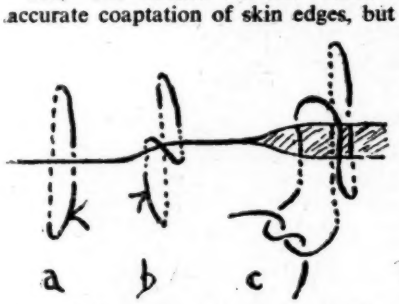
A woman aged 39 complained of vaginal discharge and pain in the left groin. The discharge was sometimes bloodstained and offensive and had been present for 13 years. She had had an upper-segment caesarean section 13½ years before, the operation being performed because of toxaemia. She was sterilized seven years ago and had had a dilatation and curettage performed four years ago. On August 3, 1949, a dilatation and curettage was performed by Mr. Mortimer Reddington, when about 4 in. (10 cm.) of thread was pulled out. The bleeding persisted and so a hysterectomy was performed and the uterus found to contain a very neat layer of sutures, except for one with a knot at the end running into the uterine cavity. There was also a small fibroid in the fundus, and the left ovary was removed at the same time.

Mr. Reddington has recalled another case which kept coming back and back with an infected wound and from which was removed finally a piece of thread about 2 ft. (61 cm.) long.—I am, etc.,

Dartford, Kent. M. NEAL RANKIN.

A Modified Skin Stitch

SIR,—The vertical mattress suture is widely used to obtain accurate coaptation of skin edges, but where thin skin overlies an excessive amount of fat, as sometimes happens, for example, in the axilla and groin, gaping of the edges tends to occur and small lobules of fat bulge through the gaps in the incision. The modification of this suture, illustrated herewith, in which the superficial portion of the stitch is reduplicated, has been found of value in holding the edges together. A small "S-bend" is produced by each stitch, but this straightens out when the silk is removed.—I am, etc.,

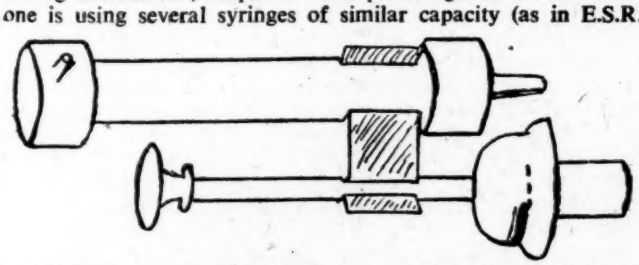


A.—Ordinary mattress suture. B.—Modified mattress suture. C.—Modified suture placed.

Birmingham. J. W. RIDDOCH.

A Clip for Syringes

SIR,—It is generally admitted that syringes and their pistons are not interchangeable. A badly fitting piston renders the syringe useless when required for aspirating fluids. To obviate this nuisance I have devised a simple double metal clip which, during sterilization, keeps the three parts together so that when one is using several syringes of similar capacity (as in E.S.R. estimations) it is impossible for them to become detached and subsequently fitted to their wrong units. The clip is so small that it does not need to be detached while the syringe is in use. Messrs. C. F. Thackray, Park Street, Leeds, can supply these clips.—I am, etc.,



Leeds. DAVID A. HERD.

Orf in Man

SIR,—I was most interested to see the letter from Drs. A. Lyell and J. A. R. Miles (November 11, p. 1119). My attention was first drawn to the condition by Dr. Ian Macquarrie when I came here as his assistant over 25 years ago. He recognized it as being an infection due to contact with sheep. A specimen of the lesion was sent for pathological examination, but its exact nature was not established. I must have seen upwards of 30 cases since then, the last a month ago.

The lesion is invariably single, and seems to confer immunity, as the condition has not occurred twice in the same person. With the exception of two cases all my patients have been males, and the lesions have been on the hand or forearm. The two exceptions were small girls who had pet lambs. In one case the lesion was on the upper lip, and in the other on the leg. At first sight the condition looks alarming, but, as mentioned in the letter, one is struck by the comparatively little pain and the absence of any general reaction. The temperature has been normal in all cases in which it was taken. The glands connected with the area of the lesion are often enlarged, but do not go on to abscess formation. Rarely has a definite history of trauma been obtained, but, as one patient said, "We are always getting pricks and scratches at farm work."

Treatment by slicing off the top of the blister, applying hot foments, and cauterizing the lesion daily with copper sulphate shortens the duration of incapacity. The condition, in my experience, is not so very rare, and, now that Drs. Lyell and Miles have proved it definitely to be orf, I think it should be added to the list of scheduled diseases.—I am, etc.,

Aspatria, Cumberland. A. K. RANKIN.

Mass Radiography

SIR,—Critics, mainly in London and Birmingham, have been scathing, almost vicious, in their denigration of mass radiography. Fortunately their efforts have not been crowned with success and the work advances. I do not wish here to defend mass radiography; it does not need it. Those who have been engaged in the work during recent years have no doubt concerning its value or of the high position that it holds in the armament against pulmonary tuberculosis.

The critics often say that the receipt of a satisfactory report on a miniature film is apt to engender a false sense of security. It is argued that as a result warning symptoms will tend to be overlooked during subsequent months. There is considerable weight in this argument and it applies equally to the satisfactory report on either a miniature or a full-size film. It depends for its validity on two factors. First, it is insufficiently realized that pulmonary tuberculosis may develop with great rapidity, cavitation, perhaps in both lungs, appearing within a few months. Secondly, that rapidly developing cases are frequently unaccompanied by any disturbance in general health. In many cases the symptoms of pulmonary tuberculosis are conspicuous by their virtual absence. In this country there is at present one at least out of every 500 adults who is suffering from active tuberculosis and in need of treatment, a potential menace to his Mantoux-negative contacts, whose general health and sense of well-being is so good that medical advice has not been sought. Some form of routine radiography of large numbers, whether on large films, miniature films, or fluorescent screen, offers the only hope of an early diagnosis.

But there is a large group of patients in whom the disease is usually more advanced, who are already attending their doctors, and, because of the triviality of their symptoms and absence of physical signs, are being treated as cases of upper respiratory tract infection. It is with these cases that there is room for improvement in the management of pulmonary tuberculosis, for failure to refer them for radiography condemns many such patients to the consequences of pulmonary cavitation which early diagnosis, adequate bed rest, chemotherapy, etc., would avert. Experience with mass miniature radiography, in spite of what they say about it, leads one to support most strongly those of your subscribers and correspondents who have been advocating that much greater attention should be paid to the symptomatology of tuberculosis and that greater use should be

made of the chest clinic x-ray apparatus. Any doctor who fails to send for a chest film a patient suffering from the symptoms of a respiratory tract infection of longer than three weeks' duration runs the grave risk of missing a case of tuberculosis. Your correspondents have on several occasions given lists of suspicious symptoms. It is not necessary to mention them again here. I have mentioned only those which are in my experience the commonest. Large film and screening sessions should be part of the weekly routine of a chest clinic, and doctors should feel free to send to it any case that arouses the slightest suspicion. I do not think it is far from the truth to say that one adult per 1,000 of city populations is being treated for respiratory tract infections when all the time pulmonary tuberculosis, perhaps remarkably far advanced, is the cause of the trouble.

If in the next five years we are to progress with the early diagnosis of pulmonary tuberculosis, then it is imperative that existing radiographic facilities be greatly improved and used more than they are to-day. At present emphasis is on treatment. In the near future, by the widespread use of routine radiography and B.C.G. we should shift the emphasis to where it rightly belongs—prevention.

In spite of the declining case mortality during the past 50 years pulmonary tuberculosis still remains supremely the major medical problem of the day. As a result of the appalling havoc it causes in the lives of so many tens of thousands of young adults, it should receive the respect that it deserves and which I feel it is still not receiving.—I am, etc.,

Buckhurst Hill, Essex. THOMAS PAXON.

Child Welfare—Past, Present, and Future

SIR,—Professor A. Moncrieff (October 7, p. 795) criticizes the pattern of child-welfare work under local authorities as being geared to vital statistics of thirty or forty years ago, while he himself uses the decline in breast-feeding as a stick to beat the service, which he summarizes as being "largely continued as part of a campaign to reduce deaths in infancy from digestive disorders."

About fifty years ago the prevalence of artificial feeding was considered to have contributed to the rise in deaths from diarrhoeal diseases (Tatham, 1904). In 1906 Newman stated that epidemic diarrhoea was the most destructive of all diseases attacking children under 5 years of age, and it was being shown (Matthew Hay, 1907–8) that the excessive mortality in bottle-fed babies was proportionately greater in the one-roomed houses. It was then easy to point the moral. During the next twenty years numerous investigations were undertaken to discover the cause, although we are still in doubt, but by the mid-1920's the proportion of infant deaths due to digestive disorders had fallen to 10% in the larger Scottish towns, although it remained a serious problem longer in the English towns. This has fallen steadily ever since, apart from a slight rise during the last war when, with exceptions (Glasgow, 1944), the outbreaks have been in hospitals and other places where children are congregated together. The improvement in general education, the increase in personal cleanliness, and the rise in the standard of living are probably the main reasons why deaths from digestive disorders are no longer a menace to the baby in its own home. The educational influences of the public health services are usually given some of the credit, although the child-welfare services as such were only in their infancy in the 1920's.

The decline in breast-feeding had a good twenty years' start on the child-welfare services, and although I am not convinced that child-welfare officers do not encourage breast-feeding whole-heartedly there is no justification for going all righteous about it. After all, the child-welfare medical officers and health visitors come on the scene after the hospitals, midwives, and general practitioners. The bigoted medical officer who is "whole-hearted," instead of helping the anxious mother who is having feeding difficulties, will make her feel a criminal if she is not breast-feeding, and will now be able to quote Professor Moncrieff that she is fulfilling her proper task in the community. America is held up as an example of a country which has reduced its infant mortality more rapidly than Great Britain. What is its record in breast-feeding?

Professor Moncrieff raises so many hares it is impossible to chase them all. He does not seem to have made up his mind whether he would rather have the medical part of the service run by general practitioners, assisted in the nursing of sick children by the health visitor, who is apparently to displace the present specially trained home nurse, or by specialist paediatricians as envisaged in circular 118/47; but, if the latter, is the paediatrician (who does not realize the value of routine medical inspections in getting to know the child and its mother, noting the progress made over a period and using the opportunity to assess the mother's care and standard of nutrition) going to interest himself in sanitation of schools, the present school curriculum, or even school meals and hygiene? The present school medical officers do these things, but then they are specialists in school medical work, not specialists in diseases of children.

The main idea is that the present maternity and child-welfare officers and school medical officers should disappear. This, as Professor Moncrieff says, is implicit in circular 118/47, which has a good deal to answer for in producing frustration in the service. Before it was suggested by obstetricians and paediatricians that maternity and child-welfare and school medical work was a boring routine and soul-destroying, and how much more interesting it would be if the participants did either (*a*) obstetrics or (*b*) paediatrics, the majority of medical officers did not find their work boring: they had chosen to do preventive work, and after several years' experience of it they found it absorbing. It is uncertain what proportion of doctors is equally interested in preventive and in curative work, but in my opinion it is only a minority, and if the present trend continues the amount of preventive work done will decrease.

After the issue of circular 118/47, and action which is being taken as a result of this circular, medical officers in the public health service find their status is falling. Having trained themselves to do one job they are now being told to go and do something else. No longer are they to have the opportunity of acquiring an insight into the whole field of maternity and child-welfare and school medical work, studying the family as a whole. They must specialize and keep themselves abreast of the times. It will be so much more interesting for them. At the same time they must not refer a child direct to a specialist, that is the privilege of the general practitioner; and, although the preventive services never dealt much in drugs, should the medical officer consider that a mother or child should benefit by medicine, the mother must now be sent on a second journey to the general practitioner. Is it surprising that there is frustration and that those already in the service are advising their younger colleagues to choose another branch of medicine?

Professor Moncrieff tells us that forward-looking authorities and progressive medical officers have already adopted the suggested changes. As far as maternity and child-welfare and assistant school medical officers are concerned they will presumably progress presently out of the public health service altogether into the ranks of the obstetricians and paediatricians.—I am, etc.,

Chelmsford. HILDA MENZIES.

REFERENCES

Hay, M. (1907–8). *Special Enquiries on Infant Mortality.* Appendices to Annual Reports, Medical Officer of Health, Aberdeen.
Newman, G. (1906). *Infant Mortality.* London.
Tatham, J. F. W. (1904). *Report of Inter-Departmental Committee on Physical Deterioration.* London.

Factory Doctors in the Health Team

SIR,—Various correspondents have stressed the value of school medical examinations and the need for closer teamwork between public health medical officers, general practitioners, and other health workers. No one so far has mentioned the appointed factory doctor. Since nearly a quarter of a million children enter industry each year, the importance of close liaison between the school medical service and the appointed factory doctor is clear. It must be rare for a general practitioner to know the work or conditions of employment of more than a handful of the youngsters for whose health he is responsible. They come for cure when ill, but otherwise may remain for long in subnormal health. Close team-work of the school medical officer, appointed factory doctor, and general practitioner would appear to offer great opportunities for health promotion and prevention of disease. Employers as well as parents and youngsters are often in need of advice and grateful for assistance.—I am, etc.,

Farnham Royal, Bucks. M. E. M. HERFORD.

Teething

SIR,—May I take the liberty of stating that not all paediatric teachers would agree with the opinion expressed in "Any Questions?" (October 28, p. 1013) that many ailments of an infant are connected with teething? Professor Von Pirquet and Professor Schick, of the Vienna University medical school, who were my teachers, would invariably emphasize in their lectures that there was no proof at all that any ailment could be traced to teething. They used to state that infants would get all the illnesses mentioned in the quoted reply from birth on, whether teething or not. For the general practitioner it may be a purely theoretical problem, since he will treat the little patient for the symptoms he notices. The danger lies with the mother, who will too easily consider her baby's illness as a "teething trouble" and neglect to ask for her doctor's advice in good time.

Besides that, the problem seems to be a very interesting one, deserving a thorough investigation. May I add a few abstracts from translated quotations?

"Teething is a physiological process without any disturbance." (H. Finkelstein, *Lehrbuch der Säuglingskrankheiten*, 2nd edition, Berlin, 1921, p. 646.)

"If one takes the trouble to watch the teething of healthy infants one would never be able to state with any authority that anything abnormal was related to teething." (Rudolf Fischl, *Diseases of the Mouth in Childhood*, in *Handbuch der Kinderheilkunde*, edited by M. Von Pfaundler and A. Schlossmann, 3, p. 35, 3rd edition, Leipzig, 1924.)—I am, etc.,

Plymouth. H. M. TIETZE.

Wrong Use of Fenestration Operation

SIR,—A good deal has been written and spoken lately about the surgery of otosclerosis. I greatly fear that this operation is being performed in this country on cases that are not otosclerosis. No case should be diagnosed as such in which a radiograph of the labyrinth has not been taken and the characteristic condition of the bone seen. I have quite recently been consulted about a case which was not otosclerosis, and in which both sides had been operated on without any good result.—I am, etc.,

Bath. H. NORMAN-BARNETT.

R.M.B.F.

SIR,—As Christmas Day is near at hand I would like to remind your readers of our Christmas Gifts Fund in the hope that those who have not sent their contributions will now do so quickly. We must not fail in bringing happiness and extra comforts to our beneficiaries.

Contributions should be sent to Royal Medical Benevolent Fund, 1, Balliol House, Manor Fields, Putney, S.W.15, marked "Christmas Gifts," and will be gratefully acknowledged.—I am, etc.,

C. LUTHER BATTESON,
Honorary Treasurer,
Royal Medical Benevolent Fund.

POINTS FROM LETTERS

Employment of Epileptics

Dr. H. A. JOHNSON (Cheltenham) writes: The sorry plight of epileptics needs investigation and most sympathetic help. . . . They need training and work in specialized factories, living either in their own homes or in hostels, with facilities for transport. They also need financial assistance when unable to work. Epileptics are the unwanted in our midst, living wretchedly unhappy lives. Medicine has failed to cure, but there is no denying the presence of hundreds of inarticulate sufferers and outcasts.

Exercises in the Bath

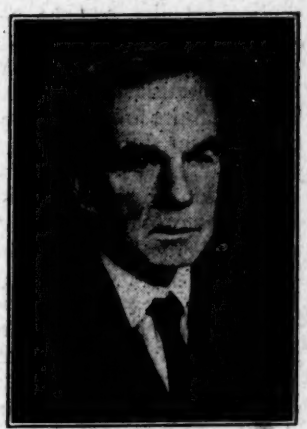
Dr. S. SHUBSACHS (Manchester) writes: Sir Leonard Hill (November 18, p. 1153) does not mention the temperature of the water. I take this to be an accidental oversight, as Sir Leonard must be more aware than most people of the effect of temperature on oxygen consumption and carbon dioxide output, which is what he has estimated.

Obituary

J. A. MURRAY, M.D., F.R.S.

Dr. J. A. Murray, one of the pioneers of experimental cancer research, died in Hove on November 20, aged 76 years. For 32 years he worked in the laboratories of the Imperial Cancer Research Fund, and for the last 20 of those years he was its director.

James Alexander Murray was born at Cramond, Midlothian, in 1873. He received his early education at the George Heriot College, and subsequently entered Edinburgh University as a science student. After graduating B.Sc. in natural science, he won a scholarship which enabled him to go to Germany and engage in zoological research work. During the summer sessions of 1895–7 he worked with Professor Theodor Boveri in the Zoological Institute of the University of Würzburg. His main problem was to study in molluscan spermatocytes the cytoplasmic structure then known as the Nebenkern and later as the Golgi apparatus. He also spent some time in Professor R. Wiedersheim's laboratory at Freiburg im Breisgau, working on the morphology of the amphibian vertebral column. On his return to Edinburgh he was appointed assistant to Professor J. Cossar Ewart in the department of zoology. At the same time he studied in the medical school of the university, and in 1899 took the degrees of M.B., Ch.B. During the next four years he had experience of general practice, and was for a period medical officer of a mental hospital. But the decisive decision of his career was made in 1903 when he accepted the invitation of Dr. E. F. Bashford to join him in the work of organizing the experimental investigation of malignant disease, a task with which the latter had been entrusted by the then recently constituted Imperial Cancer Research Fund. Here Murray found his real bent. In addition to his medical training, he brought to this work a profound interest in cellular biology, which had been stimulated by his association with Theodor Boveri, and a wide knowledge of zoology and comparative anatomy gleaned from his early student days. Murray proceeded M.D.(Edinburgh) in 1907, with the award of a gold medal. In 1915 he was appointed director of the Fund, and 10 years later he was elected a Fellow of the Royal Society. In 1936, the year after his retirement, he was awarded the Honorary Medal of the Royal College of Surgeons.



Walter Stoneman, London.

We are indebted to Dr. R. J. Ludford for the following appreciation: The initial work of the Imperial Cancer Research Fund, which was published in detail in its scientific reports, laid the foundations of experimental cancer research. It demonstrated that cancer was widely distributed among the various races of mankind and occurred also in vertebrate animals, in which it presented the same essential features. The various aspects of tumour transplantation, which had been opened up by the work of Jensen, were explored with meticulous care, and it was conclusively established that the successful transplantation of tumours in laboratory animals was dependent upon the

survival and growth of the malignant cells of the grafted tissues. Cancer was thus shown to be essentially a cellular problem. One of the most significant of Murray's contributions to cancer research, in view of later developments, was his discovery that in female mice with an immediate cancerous ancestry breast cancer was more than twice as frequent as in mice without such an ancestry. His observations extended over only three generations, but it is of interest to recall that in a paper communicated to the Royal Society in 1911 he stated, "It should be possible by continued selective mating to breed two strains of mice with a still greater difference in their liability to cancer." He lived to see this prediction amply confirmed.

Apart from his cancer investigations Murray attained distinction in other fields of scientific research. During the first world war he undertook the duties of honorary pathologist to the Zoological Society, and was elected a life Fellow of that society in appreciation of his valuable work. At the Annual Meeting of the British Medical Association in Newcastle-upon-Tyne in 1921, he was vice-president of the Section of Pathology and Bacteriology. He was an enthusiastic microscopist, and took a very active part in the affairs of the Royal Microscopical Society, being its president during the periods 1928–9 and 1946–7. Only last year he was elected to its honorary Fellowship in recognition of his distinguished services to the society and to microscopical science. As a tribute to him, the *Journal of the Royal Microscopical Society* published an issue in June this year containing seven papers by former colleagues on the staff of the Imperial Cancer Research Fund. Murray zealously maintained the highest traditions of scientific research in the academic spirit of freedom and toleration. He welcomed clear and decisive expressions of opinion, believing it was better to be proved wrong than misunderstood. He detested ambiguity, and was implacable in his opposition to anybody or anything that he considered in any way dishonest. A loyal and generous friend, he was always ready to share his scientific knowledge and experience with anyone willing to learn from him.

He married in 1927 Ethel Emily, daughter of the late L. Beere, Esq., and to her is extended the deepest sympathy of his many friends and former colleagues.

ALEXANDER LOW, M.D., LL.D.

Dr. Alexander Low, emeritus professor of anatomy in the University of Aberdeen, died in Aberdeen on November 15, aged 82 years.

Alexander Low was born of good farming stock on the estate of Grandhome on the banks of the River Don, within sight of the farms that saw the birth of Sir David Ferrier and Sir Arthur Keith. At Aberdeen University, which he entered in 1886, he first studied arts, and, after taking his M.A., he turned to medicine and graduated M.B., C.M. in 1894. He proceeded M.D. with highest honours in 1912. He became a member of the staff of the anatomy department of the University in the same year that he graduated, and was appointed professor in 1925. Although he retired in 1938 he maintained his connexion with the university and its students by serving on various committees until the last. He was a past president of the Anatomical Society of Great Britain and Ireland, of the Aberdeen Medico-Chirurgical Society, a director of the Aberdeen Royal Infirmary, a governor of the Royal Mental Hospital, and a member of the Scottish Universities Board. He had an international reputation for his research upon the development of the lower jaw. His histological technique was most accomplished, and his preparations were exquisite. Thanks to his enthusiasm the Anthropological Museum of Aberdeen University probably possesses the finest collection of the skeletal remains of the Short Stone Cist or Beaker People. For many years he made careful measurements of the growth of people born and bred in the north-east of Scotland. Certain twins and triplets he measured annually from infancy to 20 years of age.

When he retired from the chair in 1938 his former students presented him with a portrait etching, and on this occasion many touching tributes were sent by his pupils from the four corners of the world. During his office as dean of the medical faculty in Aberdeen he was responsible for welding the union of clinical professorships with ward appointments. Professor Low took an active part at several Annual Meetings of the B.M.A. At Belfast in 1909 he was secretary of the Section of Anatomy and Physiology; at Birmingham in 1911 vice-president of the Section of Anatomy and Physiology; and at Aberdeen in 1939 he was president of the Section of Anatomy and Anthropology. In the same year Aberdeen University conferred on him the honorary degree of LL.D.

We are indebted to Professor R. D. Lockhart for the following appreciation: Alexander Low had qualities that endeared him to generations of students: serious grey eyes with a pleasant twinkle set in handsome and distinguished features; an earnest purpose; attention to detail in all his work; a gentle unassuming personality; a word that could be depended upon to stand the test of time; courtesy to all people, and a kindness to his pupils in sickness or difficulty that invariably took practical form. He would find time to visit students in hospital, and, always unobtrusively left, there would be a parcel of food and sweets and cigarettes. If a man were hard up some bursary fund would be found to help, and a fine new overcoat might appear—from a "fairy godmother" for all the student knew. Many graduates will remember him as an examiner and how he would soften the blow with his characteristic, "Well, maybe, perhaps, but one usually finds . . ." No wonder he was so affectionately known as "Daddy" Low. Certainly our university will not dip her pennant in salutation to a more loyal and devoted son, and at the news of his passing the eyes of many of her graduates will be filled with wistful and happy memories.

With the passing of Dr. WILLIAM HUGH STEELE on November 1 at the age of 79 South Devon has lost a well-known figure and a remarkable personality. He was a native of Torquay and studied medicine at Edinburgh University. After graduating M.B., C.M. in 1895, he became a pioneer in radiography, and took the first *x*-ray apparatus to the relief of Ladysmith in the Boer War. After returning to this country he settled in general practice in Torquay and remained there until the outbreak of the 1914–18 war, when he again joined up and returned to radiography, serving in France and later at Plymouth. For health reasons he did not return to general practice after demobilization but took up the study of radiology and obtained the D.M.R.E. (Camb.) in 1927. He was appointed radiologist to Newton Abbot Hospital, and it is in this post that he will be best remembered by the people of South Devon and by the medical men in the district, who were always welcome and received every assistance in any problem submitted to him. His skill and kindness were outstanding qualities which testified his greatness and cannot be forgotten by a host of grateful patients and colleagues. He took a full part in all medical activities, and was a member of the British Institute of Radiology, a past chairman of the Torquay Division of the B.M.A.; and a past president of the Torquay and District Medical Society. Although he did not approve of the N.H.S. Act, he served on the house committee of Newton Abbot Hospital until his death. All his life he was a sportsman, and as a raconteur of his experiences in all

spheres he was inimitable. As a youth he played rugby football for a Torquay side, but his real loves were horses and hunting, and in the summer he delighted in trout fishing. All these pursuits he took up with an infectious enthusiasm. He married Miss Potts-Chatto, who survives him and to whom our sympathy is extended.—D. C.

Dr. JAMES KILIAN PATRICK CLARKE died at Nottingham after a long illness on November 1, aged 64. Born in Bray, Ireland, he graduated M.B., B.Ch. at the Royal University of Ireland in 1908. He settled in England in 1909 and obtained the D.P.H. in 1910. Between 1910 and 1914 he worked in mental hospitals, first at the Bethlem Hospital, Lambeth, and later at Hill End Asylum in Hertfordshire. During the 1914–18 war he served with the R.A.M.C. in Egypt, and it was in this period that he first became interested in bacteriology. After the war he was appointed lecturer in pathology at the Egyptian Government Medical School, holding also the post of bacteriologist to the Citadel Military Hospital in Cairo. In 1921 he obtained the D.T.M.&H. (Cambridge). On returning to this country in 1923 he took up research into the aetiology of dental caries, working at St. Mary's Hospital for the Medical Research Council. He published the results of this work in 1924 in a paper entitled "The Bacterial Factor in the Aetiology of Dental Caries." In 1925 he was appointed the first pathologist to the Ransom Memorial Laboratory of the General Hospital, Nottingham, a post which he held for 24 years until his retirement due to ill-health in 1949. His main interest, however, remained in the field of bacteriology, and he helped very considerably in the development of vaccine therapy while this was in vogue. At his desk or bench Clarke had a rare power of concentration upon the problem in hand. Outside the laboratory he relaxed into the most natural and friendly of men, eager to give a helping hand to anybody. One of his activities was to give pleasure to others as a topographical lecturer—a recreation in which his Irish relish for a well-turned anecdote found free play. He was a keen freemason and a member of Lodges in Nottingham, London, and Egypt. He leaves a widow, two sons, and a daughter. The elder son is a member of the medical profession.

Dr. CHRISTOPHER ROLLESTON, formerly county medical officer of health for the county of Rutland and the Soke of Peterborough, died at his home at Ketton, Rutland, on November 19, aged 73 years. Rolleston came of a distinguished medical family. His father, George Rolleston, was Regius Professor of Anatomy at Oxford University; his eldest brother was the late Sir Humphry Rolleston, and another brother was the late Dr. J. D. Rolleston, well known as a specialist in infectious diseases and as the author of many books and papers on medical subjects. Christopher Rolleston was a student at New College, Oxford, to which he won a science exhibition, and Charing Cross Hospital, where he was a university scholar. He graduated M.B., B.Chir. in 1903, proceeded M.D. in 1907, took the D.P.H. in 1909, and became a Member of the Royal College of Physicians in 1910. For a time he worked as assistant county medical officer for Berkshire, but in 1910 he was appointed county medical officer and school medical officer for Rutland. Two years later the appointment of county medical officer for the Soke of Peterborough was combined with the Rutland post. He partially retired in 1948, but he continued to act as school medical officer for the rural schools in Peterborough until December 1, 1949, his last report on school health being but recently published. Rolleston was a keen clinician, being particularly interested in tuberculosis. He was one of the earliest to undertake artificial pneumothorax treatment regularly, and was probably the first tuberculosis officer in the country to induce such treatment in the homes of his patients. The first article he published on this subject appeared in 1918, and he described the results of treating 50 cases in a paper which appeared in *Tubercle* in 1924. He was also in charge of the local V.D. clinic. He wrote on many medical subjects in this and other journals, and his annual reports usually contained some original observations about the health and social conditions of the people in his area. He was never afraid of saying what he thought—a characteristic which was not always appreciated. He was a member of the B.M.A., being chairman of the Soke of Peterborough Division in 1935–6. Apart from his work, his main interest was in literature, especially history. He was a member of the Peterborough Historical Society, before which he read a number of papers. Rolleston was twice married; he left no children.

Mr. Richard Battle writes: HUGH POMFRET KILNER, the son of Thomas Pomfret Kilner and the late Olive Mary Kilner, died suddenly in the R.A.F. Hospital, Fayid, Egypt, on November 5, aged 26 years. He was educated at Oundle School and Clare College, Cambridge. He came down to St. Thomas's Hospital in October, 1945, and graduated M.B., B.Chir. in 1949. After completing a house appointment at his hospital, he was accepted by the R.A.F. for the period of compulsory service and to his delight was posted overseas only a month or two ago. Hugh Kilner, or "Pomf" as he was known to all, was a fellow with a delightful personality. He never achieved high academic distinction, but was by contrast a really good doctor and, like his father, was intensely interested in the patients under his care and in the human side of medical practice. He took a very special interest in children, and had he been allowed to return from his Service would probably have become a paediatrician. He inherited from his mother a great talent for music, and was an accomplished pianist and a leading light in the students' Christmas show at St. Thomas's. Nobody who met "Pomf" would fail to like him, and we at St. Thomas's are much the poorer for his loss.

Medico-Legal

DEATH FROM TETANUS

A verdict of accidental death was recorded by the coroner of St. Pancras, Mr. W. Bentley Purchase, on September 22 at the inquest on Mrs. Sarah Fels, aged 50, who died in the Elizabeth Garrett Anderson Hospital, London, on August 17 from tetanus.[1]

At the inquest Mr. Bernard Fels said that in February his wife was operated upon for cancer by Mr. Vincent Nesfield. She had made a good recovery and subsequently was treated by weekly injections, usually given by a nurse. On July 19, according to Mr. Fels, Mr. Nesfield himself gave the injection at his consulting-room in Harley Street.

Some time later a swelling had developed, and on August 11 Mrs. Fels was admitted to hospital, where she died six days later from tetanus. Pus from an abscess in her leg contained *Cl. tetani*, and the same organism was recovered from the bottle from which the injections had been given.

Mr. Vincent Nesfield, who gave his qualifications as M.R.C.S.Eng., L.R.C.P.Lond., admitted to the coroner that his name was not on the *Medical Register*. He said that, after removal of Mrs. Fels's breast for cancer, he prepared an emulsion from part of the growth for injections to prevent a recurrence of the cancer. He denied that he had himself given any of the injections. On July 19 Mrs. Fels brought him the bottle of emulsion and said that it had been spilt and asked what she was to do. He saw that there was a deposit at the bottom of the bottle, so he added bi-creosol and returned the bottle to Mrs. Fels.

In recording his verdict, the coroner said that he was satisfied beyond doubt that death had been due to an injection from the bottle and that the injection had been made on July 19 by Mr. Nesfield.

Mr. Nesfield was struck off the *Medical Register* in 1932 after a charge of advertising and of being interested in the commercialization of a secret remedy had been found proved by the General Medical Council.[2]

[1] *Manchester Guardian*, September 23.
[2] *British Medical Journal, Supplement*, 1932, 2, 269

Medical Notes in Parliament

Fate of Registrars

On the motion for the adjournment on November 22, Dr. CHARLES HILL raised the matter of the proposed cut in registrars employed in the Health Services. In England and Wales there were 5,200 specialists, and 150 deaths or retirements from their ranks each year. There had been the hope of building a comprehensive specialist service in all parts of the country, and it seemed to him tragic that the annual increase in the number of specialists was calculated at 30 specialists a year. There were 2,800 practitioners training to be specialists, and to fit in with this policy of a tiny annual increase in the specialist establishments 1,100 of these trained or semi-trained men were to be swept out of the registrar ranks. In the only region whose case he had examined, this meant that three-quarters of the senior registrars would have to go as soon as possible after January 1, and two-thirds of the other registrars. He urged that the whole position should be re-examined, first, on the basis that if the implied undertaking that there should be a consultant service everywhere was to be carried out an increase of establishment of 30 consultants a year was insignificant; and, second, that the revised establishment of registrars was too drastic, and to take away these registrars from the hospitals would lower the quality of the hospital service for some time to come. The Ministry had calculated that the country needed 7,500 whole-time specialists. Yet it had only 5,200, most of whom were part-time, and its progress was to be at the rate of 30 specialists a year. That timid attitude would damage the hospitals from the early part of next year.

Mrs. JEAN MANN said she was glad Dr. Hill had raised this subject. The Minister's circular had come as a shock to all hospital services in the country. When she had read that circular in the *Supplement* to the *British Medical Journal* she had been shocked by its ruthless treatment of the registrars. These were blandly told there would be no promotion for them although they had served an apprenticeship, much of which had been financed by the Government. Many had taken diplomas in specialized branches, and a great deal of the expense of taking those diplomas had been borne by the Government. These registrars had been encouraged to go on by the statements of the Minister and of many Members on the Government side of the House that the Service was expanding, that everyone would be entitled to a specialist's attention, and that the country would not have nearly enough consultants and specialists to conduct the new services. Where would the Ministry get general practitioners with the expert knowledge which the senior registrars possessed? She believed that this memorandum had not been sent to the Scottish registrars. She hoped they would set the heather on fire when they received it.

Mr. NIALL MACPHERSON hoped that the Under-Secretary of State for Scotland would be able to tell the House whether the memorandum applied to Scotland. He had heard that it would apply if not from January at least in the course of next year. He added that the memorandum suggested in a callous way that surgeons and embryo surgeons, who in many cases had served long in the Forces, should go back to the Forces at a lower rate of pay than they would have received if they had stayed in the Services. They were also invited to go into the Colonial Service, which was not remunerated on the same scale.

Mr. WALTER ELLIOT said the House was entitled to know if the circular applied to Scotland, and, if not, whether the general conditions published in the circular applied in Scotland as in England.

Mrs. E. M. BRADDOCK said a lot of the difficulties of the Health Service were created when Dr. Hill was in an important position in the British Medical Association. The difficulties were due to the fact that his organization had laid down emphatically that no full-time medical service should be provided by the Bill.

The House then rose, without any reply being made for the Government.

The Tuberculosis Position

New cases of tuberculosis in England and Wales notified in 1949 were 52,041. Mr. ANEURIN BEVAN said on November 16 that he thought there had been an increase compared with 1948 but that the increase was due to the use of mass radiography. Although the increase in the notifications of respiratory tuberculosis was 5½%, there had been a decrease in the number of deaths over the last five years of 12½%. Treatment was resulting in a reduction in the number of fatalities. The general overall position was improving. Since the issue of a circular asking hospital authorities to make beds available for tuberculosis cases in general hospitals there had already been a large increase in the number of beds. He would be able before long to give a report on the progress made in making beds available.

Miss MARGARET HERBISON stated on November 14 that a visit by two officials of the Scottish Office to Switzerland for the purpose of inquiring into the treatment of tuberculosis was sufficiently encouraging to justify a further visit by clinical experts, arrangements for which were being put in hand.

Answering Mr. Walter Elliot, Mr. BEVAN said on November 16 that he was prepared to consider making use of the beds available in Switzerland, but that currency difficulties were involved.

Reducing the Doctor's List

On November 13 Mr. EDWARD HEATH raised the question of the reduction of doctors' lists of patients. He said that in the Borough of Bexley one doctor had been told that his list had to be reduced and 800 patients had to find another doctor. This was also happening all over the country. He hoped that his raising the matter would result in the welfare of the patient receiving full consideration in the administration of the regulation, which was not happening at present. As the result of this doctor declining to alter his list or to take a partner the county executive council had the job of cutting the list. It drew an ellipse round the area which included both his surgery and branch surgery so that it would take in the maximum of 4,200 patients. After that it sent a notice to every patient who lived outside the area, saying, "You are struck off Dr. Green's list seven days from to-day. You are given notice that in seven days you must find another doctor by going to the Post Office and there looking at the list of doctors in the borough." Mr. Heath said that meant that patients with a long relationship with that doctor were suddenly told that this relationship was ended. One constituent who with his family had for 26 years been attended by this doctor was told that he must find another. So was an old lady of 73 who had had this doctor for 15 years. Mr. Heath asked whether it was necessary suddenly to reduce this doctor's list of 5,000 to 4,200. He understood that the general turnover of a doctor's list varied between 300 and 600 patients, so he asked if the list could not be closed and left to reduce itself in about a year and a half to about 4,200. If the Minister insisted on suddenly reducing the list Mr. Heath suggested that those who had joined the list last should be the first to go. Members of families of long-standing patients should not be struck off. The doctor could provide the information required, and an attempt should be made to get it. In striking the patients off the list at seven days' notice the local executive council had been callous. It was wrong that administrative convenience should be placed before the welfare of a patient.

Mr. N. N. DODDS said the way this matter had been handled was an example of soulless bureaucracy and was bringing the Health Service into disrepute.

Mr. A. BLENKINSOP said he did not think the wording of the circular sent out by the executive council was the best that could have been desired. Had the doctor concerned tried to help the executive council, as most doctors had tried to help in carrying out the general decision on limitation, the Ministry would have been able to avoid a great deal of difficulty which had arisen. A doctor mentioned by Mr. Maudling, the Member for Barnet, had co-operated to the extent of suggesting those names which came latest on the lists. Not having the assistance of the doctor, the executive council in the Bexley case had taken what was on the whole a reasonable decision,

to rule out those patients who appeared to be farthest away from the doctor's main centre of practice. He thought that executive councils should give the patients another list of doctors in the area. This had been left in the past to the discretion of the executive council, and the practice varied from one area to another. It would be desirable if this method were more generally used. He thought that one or two points might well be looked at further, but had the doctor in the case offered his assistance more, as other doctors had elsewhere, this problem would not have arisen.

Doctors for New Estates*

Miss P. HORNSBY-SMITH raised on November 16 the method of appointing doctors to the London County Council estate area known as St. Paul's Cray, which comprised over 3,000 houses to which a large population was being moved, with scope for more medical practitioners. She wished to bring to the notice of the House the manner in which these medical appointments were made. She had found that Dr. J. D. Paulett had been granted by the county council a house compulsorily acquired from a private owner, and that having got these premises he had applied to the medical practices committee, saying he had been granted the doctor's house on the estate and asking the committee to permit him to practise. Other doctors had submitted their names to the L.C.C. as wishing to practise on the estate, but only the name of Dr. Paulett appeared to have gone forward, and the medical practices committee had no option but to appoint him. Its position was obviously prejudiced when only one name was submitted and when the applicant claimed that he had the premises. It virtually had to accept the nomination of the L.C.C. The L.C.C., by deciding what doctors should be allocated a house from which they could practise, were choosing the doctors on the estate instead of the medical practices committee.

Mr. A. BLENKINSOP said that any doctor might apply to go on the list in any area, and could be refused only if the area was over-doctored. Vacancies were advertised only when a sitting doctor withdrew or when the area was classified as being under-doctored. A doctor had full liberty to apply to go in an area, and the medical practices committee could not refuse him unless it was over-doctored. Applications went to the medical practices committee through the local executive council, but applications for houses went to the L.C.C., and provisional permission to practise was granted contingent on accommodation being granted also.

Dr. CHARLES HILL said that the St. Paul's Cray case was a particular instance of a general difficulty. When a vacancy arose through the death or retirement of a doctor and the full procedure of advertisement and selection was followed, and if a doctor obtained by purchase or otherwise the use of the professional premises from which the practice was conducted, or of the only appropriate professional premises in the area, it was difficult to make effective choice of any other applicant. That way of short-circuiting a proper form of selection was a difficulty which the medical practices committee was trying to tackle. The L.C.C. should have followed another method, informed the official machinery of the vacancy, and asked for an advertisement to be published so that selection could be made through the proper channel; and, having done that, it could have allotted to the selected doctor the house it had built as the doctor's house on the estate. He asked Mr. Blenkinsop to look into the matter to protect local authorities from the invidious task of picking a doctor. The same system of selection should apply, whether the house had been built by the local authority or not.

Mr. BLENKINSOP said the matter was under consideration between the Ministry and the British Medical Association, to find some way of dealing with the difficulty.

Admitting Foreign Dentists

On November 16 Mr. S. S. AWBERY asked Mr. Bevan, in view of the shortage of dentists, to introduce legislation to enable qualified dental surgeons from European countries, who had a practice in their own countries before becoming domiciled here but were not qualified for registration, to practise here.

Mr. ANEURIN BEVAN replied that for the protection of the public the Ministry must ensure that foreign-trained dentists admitted to practise here were no less well qualified than British-trained dentists. Subject to this principle, he was about to discuss with the bodies concerned the question whether existing arrangements could be improved.

Merit Awards

Colonel M. STODDART-SCOTT inquired on November 23 whether the Medical Merit Awards Committee was permanent; how far the chairmanship was intended to be permanent; what sum it was proposed to pay the chairman; and how many awards the committee had made.

Mr. ANEURIN BEVAN replied that so far as he was aware this was a continuing body. The remuneration of the chairman was to be reviewed at the end of the third year, and at present he received 2,000 guineas. The committee had so far recommended 1,504 consultants for awards. It was not intended to publish a list of them.

Nurses for Sanatoria

Mr. R. J. MELLISH on November 23 raised the question of the shortage of nurses in tuberculosis sanatoria. A Ministry of Health spokesman had said that out of a total of 27,763 T.B. sanatorium hospital beds in England and Wales 4,409 were unstaffed on June 30 last. This spokesman went on to say that a waiting-list of approximately 11,000 people in England and Wales had tuberculosis and awaited entry into hospital. Mr. Mellish said he was a member of the South-eastern Hospital Board, and throughout the whole of his region there was an enormous waiting-list. Men had to wait on the average five months before they could hope to go to hospital, and women had to wait 10 to 12 months. The Minister had asked the regional boards to open wards in general hospitals for tuberculosis cases, but they could not get the staff. It ought to be obligatory on the General Nursing Council to insist that all student nurses should do three months in a T.B. sanatorium as part of their general training. The pay of these nurses ought to be increased more than that of nurses in general hospitals.

Mr. J. ENOCH POWELL said that the task was to restore T.B. nursing to the parity of esteem which it had lost. A nurse who had done a year in children's, fever, or mental nursing could offset that year against the length of her general training. That did not apply to work in a sanatorium. This definitely deterred a nurse from training in a T.B. sanatorium. He suggested that a T.B. nursing bonus of £30 should be available pro rata so that a nurse who did 11 months did not lose the bonus entirely. Prejudice against T.B. nursing existed in the senior ranks of the nursing profession, and there was a great deal to be done inside the profession itself in educating people about the value and interest of T.B. nursing.

Mr. ANTHONY GREENWOOD said there was need for adequate housing, especially for male nurses. The fear of infection was deep-seated among the girls, and to an even greater extent among their parents. Sputum mugs should be abolished and replaced by destructible cartons. Nurses should be freed from the duty of counting dirty bed linen and the soiled clothing of patients. There should be facilities for the cleaning of the clothing of patients who were able to walk about and work among the other patients. There should be facilities in all wards for boiling crockery and cutlery. That was of particular importance where tuberculous patients were treated in general hospitals. Lastly, there should be electrical appliances for cleaning wards. He suggested that the Ministry of Health should set up a T.B. Nursing Corps, and if possible secure Royal Patronage for it.

Mr. A. BLENKINSOP, replying for the Government, said the number of nurses still required for the T.B. service was about 2,900. B.C.G. vaccine was being made generally available for sanatoria and general hospital staffs, as well as in the domiciliary fields. This was especially important in connexion with possible contact. Special allowances for nurses undertaking T.B. work were a matter for the Whitley Council, which had agreed upon improved scales of general pay which would, he

*See correspondence, *Supplement*, p. 232.

hoped, make this nursing more attractive. Perhaps the most important question was the secondment of nurses from teaching and other hospitals to work in sanatoria. This was a matter for the General Nursing Council and not for the Ministry. It would be hardly practicable to make secondment compulsory, but the Ministry was undertaking consultations with the teaching hospitals to work out detailed plans for secondment from those hospitals. The Ministry was anxious to secure the greatest accommodation in general hospitals, provided that adequate and proper precautions could be taken against contacts, and so on. That required either separate blocks, or at least separate ward accommodation. Reports were being made to let the Ministry know what progress could be made in this way. The Ministry hoped that there would result a valuable increase in the number of immediate beds and a steady reduction in the waiting-list. For patients at home there was the question of the recruitment of nursing staff for domiciliary nursing and the proper information to all those who had the care of patients. Local health authorities were anxious to co-operate with hospital authorities in a joint attack upon this problem.

Other Steps for the Tuberculous

Mr. GERALD WILLIAMS took up the discussion again on November 24. People were dying without treatment, and others were left so late that there was little hope of their recovery. He had two or three minor suggestions, such as that for night hostels, which would probably require no trained nurses. Plenty of beds were available abroad in Switzerland, France, and Scandinavia. The cost over there, apart from the fare, would be little more than in Britain. Despite difficulty in obtaining exchange, the Government could be a little more lenient in allowing money for such a cause. The beds were there and it was wicked not to use them.

Mr. IAIN MACLEOD said the L.C.C. had been forbidden by the Ministry of Health, on grounds of expense, to build certain night sanatoria and certain hospitals for this disease, of which St. Peter's, Stepney, was an example. This could be justified only if the House was satisfied that the £400m. spent on the Health Service was being spent on more worthy objects.

Mr. A. BLENKINSOP replied. He said that facilities in Switzerland were under review, but all the information which the Ministry of Health had from that country suggested that the contribution it could make would be much smaller than Mr. Williams had mentioned. Close co-ordination was necessary of the local health authority, of the general-practitioner service through the executive councils, and of the hospitals to solve the tuberculosis problem. The Ministry had under consideration the administrative organization of the Health Service, both in respect of tuberculosis and other special fields.

School Dental Service.—At the beginning of June the number of dentists employed was equivalent to 734 full-time officers. For a complete service of dental inspection and treatment, in which every child was seen annually and all children who required treatment accepted and received it, a ratio of about one dentist to 3,000 children would probably be required. An additional 1,150 dentists would have been needed last June to give such a ratio. The immediate aim is to get the service back to its 1948 level, for which purpose some 200 additional school dentists are needed in England and Wales.

The Penicillin (Merchant Ships) Bill.—This will enable penicillin and certain other substances to be sold or supplied to and administered on board merchant ships which carry no doctor; it was introduced by the Government in the House of Lords on November 14.

Part-time Nurses.—The present total is 25,000, and was about 17,000 when the National Health Service began. The policy is to encourage their employment wherever there are serious staff shortages.

Aureomycin.—Imports from the U.S.A. during the nine months period ended September 30 totalled 140,075 grammes, apart from small quantities for sample and trial purposes.

Supply of Spectacles.—The Parliamentary Secretary to the Ministry of Health said on November 14 that there was now a reasonable delivery date for simple types of lenses, while delivery dates were steadily improving for bi-focals and other special types. There was sufficient capacity in the country to deal with demands for both the simple and the more complex types of lenses.

Universities and Colleges

UNIVERSITY OF OXFORD

In a Congregation held on October 28 the degree of B.M. was conferred, in absence, on Patience Proby.

UNIVERSITY OF CAMBRIDGE

Members of the committee for the appointment of the director of the Molteno Institute have been appointed for two years from January 1, 1951, as follows: *By the General Board*, Professor E. D. Adrian, O.M., F.R.S., and J. T. Saunders, M.A.; *By the Council of the School of the Biological Sciences*, Professor H. R. Dean, Dr. V. B. Wigglesworth, Professor G. E. Briggs, M.A., and Mr. K. M. Smith, Ph.D.

The Faculty Board of Biology "B" has elected Professor Adrian as a manager of the Arnold Gerstenberg Studentship until December 31, 1955.

The Raymond Horton-Smith Prize for 1949–50 has been awarded to Anthony Guy Everson Pearse, M.D., for his essay on "Cytochemistry and Secretory Cytology of the Anterior Hypophysis"; *proxime accessit*, Basil Gerald Parsons-Smith, M.D., whose subject was "The Value of Electroencephalographic Study in Cases of Cerebral Tumour."

UNIVERSITY OF LONDON

The Sanderson-Wells Lecture on "Food and Folly" will be delivered by Sir Stanton Hicks, professor of human physiology and pharmacology in the University of Adelaide, in the Senate House, University of London, Bloomsbury, W.C., on Thursday, December 14, at 5.30 p.m. The lecture is addressed to students of the University and to others interested in the subject. Admission is free, without ticket.

UNIVERSITY OF WALES

The following candidates for the degrees of M.B., B.Ch. at the Welsh National School of Medicine have satisfied the examiners at the examination indicated:

PATHOLOGY AND BACTERIOLOGY.—L. V. Chubb, Patricia M. Coldrick, C. W. J. Hunt, A. P. Jones, Olive C. Jones, Margaret E. Lloyd, G. K. Penn, T. B. N. Richards, Eve Wiltshaw, Isobel M. Young.

UNIVERSITY OF BIRMINGHAM

Professor C. F. V. Smout has been reappointed Sub-Dean and Tutor of the Faculty of Medicine for five years from October 1.

Professor Hilda N. Lloyd, President of the Royal College of Obstetricians and Gynaecologists, has resigned from the Chair of Obstetrics and Gynaecology in the University, as from December 31.

The title of Reader in Medicine has been conferred on Kenneth William Donald, M.D., M.R.C.P., who has been appointed Lecturer in Medicine in the Faculty of Medicine from October 1.

The title of Reader in Surgery has been conferred on Bryan Nicholas Brooke, M.Chir., F.R.C.S., Lecturer and First Assistant in the Faculty of Medicine.

Professor Edward D. Churchill, M.D., Chief of the General Surgical Services, Massachusetts General Hospital, Boston, U.S.A., has accepted an invitation to participate in the surgical work of the teaching hospitals during the Spring Term, 1951.

Mr. John A. Stallworthy, F.R.C.S., M.R.C.O.G., will deliver the Ingleby Lectures for 1951.

The following appointments are announced: *Lecturer in Bacteriology*, M. B. Conran, M.B., B.S. *University Lecturer in Minor Operative Surgery*, Alexander Innes, M.B., F.R.C.S. *University Clinical Lecturers.—Obstetrics*, Jean L. Hallum, M.D., M.R.C.O.G., D.C.H., G. S. Lester, M.B., F.R.C.S.Ed., M.R.C.O.G., L. M. Park, M.B., F.R.C.S., F.R.C.S.Ed.; *Radiology*, J. C. Bishop, M.B., Ch.B., D.M.R.D., W. H. Bond, M.B., F.R.C.S., O. E. Smith, M.B., Ch.B., D.M.R.D.; *Dental Surgery*, R. F. Pusey, M.R.C.S., L.R.C.P., B.D.S.

Isobel T. Hinde, M.B., B.Chir., and John Hardwicke, M.B., B.S., Research Fellows of the Medical Research Council, have been given the title of Honorary Research Fellow in Experimental Pathology in the Department of Pathology of the University.

UNIVERSITY OF BRISTOL

The following candidates have been approved at the examination indicated:

DIPLOMA IN MEDICAL RADIODIAGNOSIS.—*Part II:* J. B. Fox, Z. Lachowicz.

ROYAL COLLEGE OF SURGEONS OF ENGLAND

At a meeting of the Council of the College held on November 9, with Sir Cecil Wakeley, President, in the chair, Mr. W. Kelsey Fry was admitted as a co-opted Member of the Council.

Professor G. Grey Turner has been elected a Hunterian Trustee; Dr. Howard K. Gray, of the Mayo Clinic, a Moynihan Lecturer; and Professor Francis E. Stock, of Hong Kong, a Hunterian Professor. The re-election of Mr. F. Masina as Prophit Student was reported.

The Council received from Dr. G. M. Vevers a gift of a cast of the Cheselden Medal.

Diplomas in Child Health were awarded, jointly with the Royal College of Physicians of London, to S. Binder, F. S. W. Brimblecombe, and P. West. A Diploma in Medical Radio-Diagnosis was awarded, jointly with the Royal College of Physicians of London, to P. F. J. New.

The following hospitals were recognized under paragraph 23 of the Fellowship regulations: Waikato Hospital, Hamilton, New Zealand; Birmingham and Midland Ear and Throat Hospital (junior registrar); Royal Victoria Hospital, Bournemouth (four house-surgeons, orthopaedic house-surgeon, all for six months); Archway Group, London (registrar, two junior registrars, three house-surgeons, one orthopaedic house-surgeon, ear, nose, and throat registrar); Hackney Hospital, London (registrar, two house-surgeons, for six months).

ROYAL COLLEGE OF PHYSICIANS OF EDINBURGH

At a quarterly meeting of the College held on November 7, with the President, Sir David K. Henderson, in the chair, the following were elected Fellows of the College: I. C. Macdonald, R. B. McMillan.

The following were elected Members of the College: B. W. Anderson, A. A. H. Gailey, S. A. Mannan, M. Mousiquddin, P. R. Mohan, A. W. Lees, W. L. H. Jackson, S. A-K. Karagulla, E. D. Levittan, J. F. McHarg, A. B. Da Costa, D. L. Murti Rao, R. F. Brooks, A. A. A. El Sherif, S. E. Large, R. J. C. Southern, R. D. Young, J. B. Clark, N. K. Smith, M. F. G. Buchanan, J. A. McConachie, R. L. Richards, I. S. Collins, T. L. Henderson, N. H. Dalal.

The Hill-Pattison Struthers Bursary was awarded to Alan Fennell Bushby.

A presentation was made to Mr. T. H. Graham on his retirement after 40 years' service as librarian of the College.

ROYAL FACULTY OF PHYSICIANS AND SURGEONS OF GLASGOW

At the annual meeting of the Royal Faculty of Physicians and Surgeons of Glasgow, held on November 6, the following officers were elected for the ensuing year: *President*, Mr. Walter W. Galbraith; *Visitor*, Mr. Andrew Allison; *Honorary Treasurer*, Mr. Matthew White; *Honorary Librarian*, Dr. Archibald L. Goodall; *Representative on General Medical Council*, Mr. Andrew Allison.

SOCIETY OF APOTHECARIES OF LONDON

At a meeting of the Court of Assistants held recently with Dr. Frank Howitt, Master, in the chair, Mr. R. Ogier Ward resigned his seat on the Court. Dr. J. P. Hedley was re-elected as the Society's representative on the General Medical Council for a further year.

The annual Master's Day Service was held at the Church of St. James, Garlickhithe, Garlick Hill, London, E.C., on October 31, by permission of the Rector, the Rev. M. F. Foxell, Chaplain to the Master.

It was reported that the Strickland Goodall Triennial Memorial Lecture is due to be delivered in 1951.

In connexion with the Festival of Britain it was decided that the Hall should be open to visitors on certain days to be arranged and that the Society should lend some of its ancient silver to an exhibition at Goldsmiths' Hall.

The following candidates were granted the diploma of L.M.S.S.A. upon examination: C. S. Paul, H. Davidson, P. S. McClure, D. J. Müller.

CONJOINT BOARD IN SCOTLAND

The following candidates, having passed the final examinations, have been granted the diploma of L.R.C.P.Ed., L.R.C.S.Ed., L.R.F.P.&S.Glasg.: W. St. C. Bauld, T. L. Bowden, W. Brabbin, L. Brinberg, J. P. Capel, S. Caplan, J. T. Davidson, J. W. Davison, D. Duck, Ruth M. Eaton, R. Y. Forbes, Isabel M. Forster, M. Frieze, K. M. Graham, J. G. Green, A. I. Hutchinson, J. L. W. Johnson, Anna M. M. Lepper, Veronica R. E. Lethbridge, T. J. McCabe, R. H. G. McKay, I. T. McLachlan, A. M. Muir, D. Murray, P. A. O'Brien, A. Pollok, Anne McK. Rodger, B. Schulberg, H. B. Singh, P. I. Sless, B. D'A. Smith, L. Steen, I. S. Trotter, E. G. C. Valerio.

No. 45

INFECTIOUS DISEASES AND VITAL STATISTICS

We print below a summary of Infectious Diseases and Vital Statistics in the British Isles during the week ended November 11.

Figures of Principal Notifiable Diseases for the week and those for the corresponding week last year, for: (a) England and Wales (London included). (b) London (administrative county). (c) Scotland. (d) Eire. (e) Northern Ireland

Figures of Births and Deaths, and of Deaths recorded under each infectious disease, are for: (a) The 126 great towns in England and Wales (including London). (b) London (administrative county). (c) The 16 principal towns in Scotland. (d) The 13 principal towns in Eire. (e) The 10 principal towns in Northern Ireland.

A dash — denotes no cases; a blank space denotes disease not notifiable or no return available.

Disease	1950 (a)	(b)	(c)	(d)	(e)	1949 (Corresponding Week) (a)	(b)	(c)	(d)	(e)
Meningococcal infection	26	3	11	2	1	20	2	10	2	—
Deaths		1	—				1	—		
Diphtheria	55	1	15	4	2	85	10	23	3	4
Deaths	—	—	—	—	—	—	—	1	—	—
Dysentery	411	61	146		6	92	12	87	4	1
Deaths		—			—				—	—
Encephalitis, acute	3	—	—		—	—	—	—	—	—
Deaths		1		—			—			
Erysipelas			25	9	3			40	4	6
Deaths							—			
Infective enteritis or diarrhoea under 2 years				42	20				55	
Deaths	17		3	1	1	20	—	10	8	1
Measles*	8,857	544	195	100	120	1,055	48	38	80	58
Deaths†		—	—	—	—			—	1	—
Ophthalmia neonatorum	26	4	13		—	21	1	6	—	—
Deaths										
Paratyphoid fever	3	—	1 (B)		—	7	—	4 (B)	2 (B)	—
Deaths	—		—		—	—	—	—	—	—
Pneumonia, influenzal	465	20	2		16	534	18	6	1	11
Deaths (from influenza)‡	20	3	3	1	—	21	8	1	—	—
Pneumonia, primary			146	¶				173	17	
Deaths	177	23		5	13	207	44		13	8
Poliomyelitis, acute	225	11	22	1	4	316	47	2	6	—
Deaths§	9	1		—		20	3			
Puerperal fever			8				—	3		
Deaths										
Puerperal pyrexia‖	82	6	5	1	1	90	11	8	—	—
Deaths							—			
Relapsing fever	—	—			—	—	—			—
Deaths										
Scarlet fever	1,206	99	199	104	55	2,163	190	253	148	193
Deaths†		—	—	—	—			—	—	—
Smallpox	—	—	—		—	1	—	—	—	—
Deaths					—				—	—
Typhoid fever	3	1	1	—	—	18	1	—	—	1
Deaths	—	—	—		—	—	—	—	—	—
Typhus fever	—	—	—	—	—	—	—	—	—	—
Deaths					—				—	—
Whooping-cough	3,725	285	454	64	36	977	22	55	20	39
Deaths	2	1	1	—	—	5	1	—	—	—
Deaths (0–1 year)	224	30	34	13	12	258	31	45	26	7
Deaths (excluding stillbirths)	5,101	814	635	181	129	5,389	966	612	215	102
Annual death rate (per 1,000 persons living)			12·8					12·3	13·3	
Live births	6,441	1036	768	381	174	6,710	1101	848	338	216
Annual rate per 1,000 persons living			15·4					17·0	20·9	
Stillbirths	159	26	23			170	25	26		
Rate per 1,000 total births (including stillborn)			29					30		

* Measles is not notifiable in Scotland, and the returns are therefore an approximation only.

† Deaths from measles and scarlet fever for England and Wales, London (administrative county), will no longer be published.

‡ Includes primary form for England and Wales, London (administrative county), and Northern Ireland.

§ The number of deaths from poliomyelitis and polio-encephalitis for England and Wales, London (administrative county), are combined.

‖ Includes puerperal fever for England and Wales and Eire.

¶ Primary pneumonia no longer notifiable in Eire.

EPIDEMIOLOGICAL NOTES

Poliomyelitis

Notifications of poliomyelitis in the week ending November 18 were: paralytic, 110 (161); non-paralytic, 39 (64); total, 149 (225). The figures for the previous week, compared with which there was a total decrease of 76, are in parentheses. Uncorrected notifications for the corresponding week in 1947 and 1949 totalled 201 and 229 respectively. Total uncorrected notifications for 1950 to and including the week under review are 8,121. The corresponding figures for 1947, 1948, and 1949 are 8,676, 2,165, and 6,134 respectively. The marked downward trend in the week under review is very satisfactory.

Discussion of Table

In *England and Wales* infectious diseases were more prevalent during the week, and the increases in the number of notifications included measles 1,042, whooping-cough 638, dysentery 151, scarlet fever 98, acute pneumonia 32, and acute poliomyelitis 21.

The incidence of measles during the autumn has been high, and the present level has been exceeded only in 1940 and 1942 since this disease was made notifiable in 1939. The largest rises in measles during the week were Lancashire 333, Lincolnshire 163, Warwickshire 111, Glamorganshire 108, Nottinghamshire 105, Yorkshire West Riding 105, while the largest falls were Derbyshire 87, Surrey 74, Yorkshire East Riding 59, and Herefordshire 43. The incidence of whooping-cough during the past weeks has been at the highest level for this period of the year since notification was started in 1939. The largest rises in whooping-cough during the week reviewed were Lancashire 131, Essex 69, and Middlesex 46. The chief features of the returns for diphtheria were a decrease of 4 in London and a rise of 9 in Warwickshire (11 of the 12 cases in this county were notified in Birmingham C.B.). The chief variations in the trends of scarlet fever were increases in Yorkshire West Riding 37 and Durham 23.

The chief centres of dysentery were Lancashire 69 (Liverpool C.B. 13, Manchester C.B. 10, Oldham C.B. 8, Southport C.B. 8), Leicestershire 62 (Leicester C.B. 58), London 61 (Lambeth 36), Northumberland 36 (Rothbury R.D. 29), Essex 28 (Romford M.B. 15, Leyton U.D. 10), Yorkshire West Riding 19 (Huddersfield C.B. 7), Kent 17 (Chatham M.B. 7, Orpington U.D. 7), Glamorganshire 13 (Cardiff C.B. 13), Anglesey 10 (Valley R.D. 8), Staffordshire 10.

The largest of the local increases in acute poliomyelitis was a rise of from 2 to 12 in Dorsetshire. The largest returns were Lancashire 14 (Liverpool C.B. 8), Cheshire 13 (Birkenhead C.B. 4), Dorsetshire 12, Yorkshire West Riding 12, Surrey 12 (Croydon C.B. 4), Gloucestershire 11 (Bristol C.B. 7), London 11, Devonshire 10, Cornwall 10, Warwickshire 10 (Birmingham C.B. 5), Durham 10.

In *Scotland* increases were recorded in the number of notifications of measles 64, whooping-cough 45, and dysentery 22. The notifications of acute poliomyelitis were 4 more than in the preceding week, and the largest returns were Glasgow 6 and Fife county 3. The largest centres of dysentery were Glasgow 57, Lanark county 40, Edinburgh 13, and Stirling county 10.

In *Eire* increases were recorded in the number of notifications of scarlet fever 34, whooping-cough 29, diarrhoea and enteritis 17, and a decrease of 19 in the notifications of measles. These trends were due to small variations in incidence throughout the country.

In *Northern Ireland* an increase of 49 in the number of notifications of measles was the only large fluctuation in the totals for infectious diseases. A rise in the incidence of measles occurred throughout the country; the largest was 16 in Armagh county. Only 4 cases of poliomyelitis, 5 fewer than in the preceding week, were notified. In Belfast C.B. the notifications of diarrhoea and enteritis increased by 9, but a fall of 7 was reported in the remainder of the country.

Week Ending November 18

The notifications of infectious diseases in England and Wales during the week included scarlet fever 1,386, whooping-cough 4,130, diphtheria 76, measles 10,132, acute pneumonia 558, acute poliomyelitis 149, dysentery 474, paratyphoid fever 1, typhoid fever 5.

Medical News

Annual Dinner of the Society of M.O.H.s

The Society of Medical Officers of Health held their annual dinner at the Piccadilly Hotel on November 23. The toast to the society was proposed by Dr. E. A. Gregg, Chairman of Council of the B.M.A., who referred to the strengthening of the link between the society and the Association. He marvelled at the moderation and patience of the Society, whose members steadfastly discharged their duties under conditions which it was unfair to expect them to accept. Dr. Gregg concluded with a tribute to Dr. Metcalfe Brown, chairman of the Public Health Committee of the B.M.A., and to other medical officers of health who had worked hard for the Association and the society. Dr. J. M. Gibson, president of the society, responded. He said that members of the society had been disturbed in recent years by the lack of recognition which was the due of the public health service. Above all, the N.H.S. Act had dulled their spirits, and they had been cheered by the support given by the B.M.A. He thought the pendulum was now swinging back and things were not so bad as they once seemed. Dr. Hugh Paul, proposing the health of the guests, delighted his hearers with a series of rapid-fire witticisms. He paid particular tribute to Sir George Elliston, who had done so much for public health, and to Dr. A. V. Kelynack for helping the members of the society to get what they wanted. Dr. Paul referred to the fact that their chief guest, Sir John Charles, now Chief Medical Officer at the Ministry, had once been a medical officer of health. In his reply Sir John said he saw no final definition of nor steady pattern in the work of an M.O.H. Legislation took away and added functions, but in general the tasks of a medical officer of health well befitted a man and constituted a man's work. Sir Cecil Wakeley also replied for the guests.

Dinner for Bart's Men

The Bart's men in South Africa have arranged a dinner to be held at the time of the B.M.A. Congress next year. It will take place on the evening of July 19, 1951, at the Rand Club, Johannesburg. Any Bart's men who may be visiting South Africa at that time, whether to attend the Congress or not, should communicate with Dr. J. Gluckman, P.O. Box 455, Johannesburg.

X-ray Photographs by Radio

X-ray photographs can be telegraphed overseas by means of the Post Office Cable and Wireless phototelegraphy service. This can be of the utmost importance when a doctor wishes to have an urgent consultation with a colleague in another country. The charge depends on the size of the photograph to be transmitted and also upon the country of destination. It ranges from £1 10s. for a small picture to Belgium or France up to £15 for a large one to the United States. A reply can be paid for in advance and express delivery can be arranged at a small additional fee. Full particulars can be obtained at any Cable and Wireless office and the large post offices, or by telephone to London: Temple Bar 1222, extension 282; Monarch 8060, extension 305.

Princess Tsahai Memorial Hospital, Ethiopia

Five members of the hospital staff, including the medical superintendent and the matron, have now been appointed, and a gynaecologist and nursing staff are being sought. Medical equipment has already been shipped out. Donations for the work of the hospital may still be made to the honorary treasurers, Lord Horder and Lord Amulree, care of Messrs. Gould and Prideaux, 88, Bishopsgate, E.C.2.

International Centre for Chemical Microbiology in Rome

The World Health Organization, with the consent of the Italian Government, has recognized the Istituto Superiore di Sanità in Rome as an International Research Centre for Chemical Microbiology. It is an active centre of research, the largest in Italy, and, mainly thanks to the initiative and outstanding organizing capability of its director-general, Professor Domenico Marotta, its laboratories are among the most modern and best equipped in Europe. The research departments include physics, therapeutic chemistry, biochemistry, malariology, and bacteriology. The Istituto Superiore di Sanità is also the main Food and Drug Control Centre of the Italian Government. Recent extensions of the Institute contain a fermentation pilot plant, with fermenters up to 18,000 litres capacity and all the processing equipment required for the isolation on an industrial scale of biologically important substances, such as antibiotics, enzymes, growth factors, etc. The International Centre for Chemical Microbiology will be under the scientific direction of Professor E. B. Chain, F.R.S., formerly of Oxford University, joint winner of the Nobel Prize for 1945 for his chemical work on penicillin, and recently elected first chairman of the newly formed Expert Committee on Antibiotics of the World Health Organization. The entire idea of the project was born as the result of a lecture tour which Dr. Chain undertook in Italy for the British Council in 1947.

New Antibiotic against Amoebiasis

At the first Medical Symposium on Tropical Diseases of the Middle East, held in Beirut under W.H.O. auspices on November 18 and 19, Dr. Hamilton H. Anderson, dean of the medical faculty of the American University, who had just returned from the United States, announced that a new antibiotic, called fumigillin and still in the experimental stage, had shown great potential value for the treatment of amoebic dysentery.

Science in Africa

According to *The Times*, the Scientific Council for Africa South of the Sahara, which has just concluded its first session at Nairobi under the presidency of Dr. P. J. Du Toit, is to investigate the preparation of regional maps dealing with climatology, vector-borne disease, geology, etc., and the sponsoring of development in field hydrology and water conservation. The council has delegates from South Africa, Madagascar, Portugal, Britain, British East Africa, French West Africa, British West Africa, Southern Rhodesia, Belgian Congo, and French Equatorial Africa, and is trying to co-ordinate and promote scientific work throughout the greater part of the continent. The first African Malaria Conference opened on November 27 at Kampala, Uganda, under W.H.O. auspices.

Aureomycin Made in Britain

At Hirwaun, near Merthyr Tydfil, in South Wales, a factory owned by the Lederle Laboratories division of Cyanamid Products Ltd. will shortly begin to produce enough aureomycin for home consumption and some export. By arrangement with the Ministry of Health, only the purification and packaging of the crude antibiotic imported from the U.S.A. will be carried out here, but the erection of a complete fermentation plant by Lederle, who hold the patents, is under consideration.

Lasker Awards

The American Public Health Association has announced that its 1950 Lasker awards have been given to three American doctors and to the International Health Division of the Rockefeller Foundation. These awards are made for work on diseases which are the main causes of death and disability, and for distinguished service in public health administration. The International Health Division receives the award for its outstanding achievements in the control of hookworm, yellow fever, malaria, and other infectious diseases. Individuals to whom the award has been made include Dr. G. W. Beadle, professor of biology at California Institute of Technology, for work on the control of transmission of hereditary factors in disease; Dr. G. Papanicolaou, of Cornell University, for outstanding contributions to the early diagnosis of cancer; and Dr. E. L. Bishop, of the Tennessee Valley Authority, for original work in public health administration, particularly in the reduction of endemic malaria.

Wills

Mr. Warwick Deeping, the novelist and medical man, left £33,675. Professor A. B. Appleton, emeritus professor of anatomy at St. Thomas's Hospital, left £6,879. Dr. Harman Taylor, of Liverpool, left £8,236; Dr. C. R. Harvey, of Bristol, £61,883; Dr. A. W. Young, of Boxmoor, £31,192. Mr. Eldred Moss Corner, consulting surgeon to St. Thomas's Hospital and to Great Ormond Street Hospital for Sick Children, left £15,680. Dr. Gerald D. Channell, who lost his life in a fire following an explosion at Brompton Hospital, left £3,281. Dr. A. de W. Snowden, formerly of Linford, Ringwood, left £22,683.

COMING EVENTS

FitzPatrick Lectures

Dr. William Brockbank will deliver the FitzPatrick Lectures on "The History of Some Therapeutic Procedures" before the Royal College of Physicians of London (Pall Mall East, S.W.), on Tuesday and Thursday, December 5 and 7, at 5 p.m. In the first lecture Dr. Brockbank will discuss the enema, and in the second cupping and leeching.

Third Legg Memorial Lecture

Sir Thomas Fairbank will give the third Legg Memorial Lecture at King's College Hospital Medical School, Denmark Hill, London, S.E.5, on Friday, December 8, at 4.30 p.m., and his subject will be "The Spine."

Suprarenal Cortex in Disorders of Childhood

Sir Stanton Hicks, professor of human physiology and pharmacology in the University of Adelaide, will deliver a lecture on "The Role of Suprarenal Cortical Function in Disorders of Childhood" at the Ciba Foundation, 41, Portland Place, London, W., on Tuesday, December 12, at 5 p.m., with Lord Horder in the chair. Admission is by ticket obtainable from the secretary of the Foundation at the above address.

Aberdeen University Club, London

The club is holding a dinner and dance on Thursday, December 14, at the Hyde Park Hotel, Knightsbridge, London, S.W., at 7 p.m. for 7.30 p.m., with dancing till 11.45 p.m. Tickets may be had from the secretary, Aberdeen University Club, Southern Hospital, Dartford, Kent, on or before Monday, December 11, at 25s. each.

Florence Tong Lecture

The first Florence Tong Lecture of the Association of British Neurologists will be delivered by Dr. E. C. Lumsden in the lecture theatre, National Hospital, Queen Square, London, W.C., on Saturday, December 16, at 10 a.m. His subject is "Basic Problems in the Pathology of Disseminated Sclerosis and Demyelinating Disease." Admission to the lecture is free.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Friday

WHIPPS CROSS HOSPITAL MEDICAL SCHOOL, Leytonstone, E.—December 1, 8.30 p.m., "*Vitamins and Human Beings*," by Professor J. R. Marrack.

Monday

●HUNTERIAN SOCIETY.—At Talbot Restaurant, 64, London Wall, London, E.C., December 4, 7 for 7.30 p.m., dinner meeting. "*Bad Habits in Children*," discussion to be opened by Dr. Felix Brown and Dr. Wilfrid Sheldon.

●INSTITUTE OF NEUROLOGY, National Hospital, Queen Square, London, W.C.—December 4, 5 p.m., "*Infantile Hemiplegia*," by Dr. W. G. Wyllie.

INSTITUTE OF OPHTHALMOLOGY, Judd Street, London, W.C.—December 4, 5.30 p.m., "*Spontaneous Hyphema*," by Mr. J. H. Doggart.

INSTITUTE OF PSYCHIATRY, Maudsley Hospital, Denmark Hill, London, S.E.—December 4, 5.30 p.m., lecture-demonstration for postgraduates by Dr. K. Cameron.

PHARMACEUTICAL SOCIETY OF GREAT BRITAIN, 17, Bloomsbury Square, London, W.C.—December 4, 7.30 p.m., "*Veterinary Therapeutics*," by J. Carmichael, D.Sc.

●ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London, W.C.—December 4, 3.45 p.m., "*Human Pharmacology, with Special Reference to Antihistaminics*," by Professor W. A. Bain.

●ROYAL EYE HOSPITAL, St. George's Circus, Southwark, London, S.E.—December 4, 5.30 p.m., "*Anatomy of the Eye and Orbit*," by Professor T. Nicol.

●SOCIETY OF APOTHECARIES OF LONDON, Black Friars Lane, Queen Victoria Street, E.C.—December 4, 3.30 p.m., "*The Theoretical Aspects of Isotopes in Relation to Medicine*," by Professor A. W. Wormall; 5 p.m., "*Practical Aspects of Isotopes in Relation to Medicine*," by Professor J. S. Mitchell.

UNIVERSITY COLLEGE, Gower Street, London, W.C.—December 4, 4.45 p.m., "*Aspects of Protein Structure*," by Dr. A. Elliott and Dr. W. E. Hanby.

Tuesday

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, Keppel Street, London, W.C., December 5, 5.30 p.m., "*High Blood Pressure and Renal Disease*," by Professor Clifford Wilson.

●INSTITUTE OF DERMATOLOGY, Lisle Street, Leicester Square, London, W.C.—December 5, 5 p.m., "*Pigmentary Conditions of the Skin*," by Dr. I. Muende.

INSTITUTE OF UROLOGY (UNIVERSITY OF LONDON).—(1) At St. Paul's Hospital, Henrietta Street, London, W.C., December 5, 3 p.m., ward round by Mr. J. D. Fergusson; (2) At St. Peter's Hospital, Henrietta Street, London, W.C., December 5, 10.30 a.m., ward round by Mr. H. K. Vernon; (3) At St. Peter's Hospital, Henrietta Street, London, W.C., December 5, 5 p.m., "*New Growths of the Bladder*," by Mr. J. G. Sandrey.

ROYAL COLLEGE OF PHYSICIANS OF LONDON, Pall Mall East, S.W.—December 5, 5 p.m., "*The History of Some Therapeutic Procedures: The Enema*," FitzPatrick Lecture by Dr. William Brockbank.

ROYAL EYE HOSPITAL, St. George's Circus, Southwark, London, S.E.—December 5, 5 p.m., "*Science and Art of Refraction*," by Dr. T. H. Whittington.

●SOCIETY OF APOTHECARIES OF LONDON, Black Friars Lane, Queen Victoria Street, E.C.—December 5, 3.30 p.m., "*Biochemical Considerations of the Suprarenal Gland and its Relationship to Medical Therapy, with Special Reference to Rheumatoid Arthritis*," by Professor E. C. Dodds, F.R.S.; 5 p.m., "*The Use of Steroid Hormones in Rheumatoid Arthritis*," by Dr. W. S. C Copeman.

Wednesday

●INSTITUTE OF DERMATOLOGY, Lisle Street, Leicester Square, London, W.C.—December 6, 5 p.m., "*X-ray Technique*," by Dr. C. W. McKenny.

INSTITUTE OF UROLOGY (UNIVERSITY OF LONDON).—At St. Peter's Hospital, Henrietta Street, London, W.C., December 6, (1) 3.30 p.m., museum specimens by Dr. Cuthbert Dukes; (2) 5 p.m., "*New Growths of the Bladder*," by Mr. J. G. Sandrey.

LONDON UNIVERSITY.—At University College (Anatomy Theatre), Gower Street, London, W.C., December 6, 5.30 p.m., "*The Cyto-architectonic Organization of the Spinal Cord*," by Professor Bror Rexed (Stockholm).

●NATIONAL INSTITUTE OF INDUSTRIAL PSYCHOLOGY.—At London School of Hygiene and Tropical Medicine, Keppel Street, Gower Street, W.C., December 6, 6 p.m., "*The Institute's Inquiry into Joint Consultation*," by Mrs. Winifred Raphael.

●ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London, W.C.—December 6, 3.45 p.m., "*Principles of Immunity in Relation to Surgical Practice*," by Lord Stamp.

ROYAL EYE HOSPITAL, St. George's Circus, Southwark, London, S.E.—December 6, 4 p.m., "*Clinical Ophthalmology*" (Revision), by Mr. R. A. Burn and Mr. R. P. Crick; 5.30 p.m., "*Proptosis*," by Mr. L. H. Savin.

●SOCIETY OF APOTHECARIES OF LONDON, Black Friars Lane, Queen Victoria Street, E.C.—December 6, 3.30 p.m., "*The Theoretical Aspects of the Investigation of Renal Diseases*," by Professor E. J. King; 5 p.m., "*Some Aspects of Treatment in Renal Disease*," by Professor Max Rosenheim.

Thursday

BRITISH MEDICAL STUDENTS' ASSOCIATION.—At Bearsted Theatre, The London Hospital, Whitechapel, E., December 7, 5.30 p.m., "*Travels and Experience in Australia*," by Dr. A. Peacock.

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, Keppel Street, London, W.C., December 7, 5.30 p.m., "*Dynamics of Heart Failure*," by Professor J. McMichael.

FACULTY OF HOMOEOPATHY.—At Royal London Homoeopathic Hospital, Great Ormond Street, London, W.C., December 7, 5 p.m., film: "*Varicose Ulceration: Its Treatment. Method of Bandaging Curative of Varicose Ulceration*," to be presented by Dr Stuart McAusland. Discussion to be opened by Mr. Harold Dodd

HONYMAN GILLESPIE LECTURE.—At University New Buildings (Anatomy Theatre), Teviot Place, Edinburgh, December 7, 5 p.m., "*Osteoarthritis of the Hip*," by Professor Walter Mercer.

●INSTITUTE OF DERMATOLOGY, Lisle Street, Leicester Square, London, W.C.—December 7, 5 p.m., "*Hirsutism*," by Dr. A. D. Porter.

INSTITUTE OF OPHTHALMOLOGY, Judd Street, London, W.C.—December 7, 5.30 p.m., "*Non-inflammatory Lacrimal Obstruction*," by Mr. G. G. Penman.

INSTITUTE OF PSYCHIATRY, Maudsley Hospital, Denmark Hill, London, S.E.—December 7, 3 p.m., "*Neural Control of Pituitary Gland*," by Dr. G. W. Harris.

INSTITUTE OF UROLOGY (UNIVERSITY OF LONDON).—At St. Paul's Hospital, Henrietta Street, London, W.C., December 7, 5 p.m., "*Neoplasms of the Urethra, Penis, and Scrotum*," by Mr. D. I. Williams.

LONDON COUNTY MEDICAL SOCIETY.—At New End Hospital, Hampstead, London, N.W., December 7, 3 p.m., clinical meeting.

ROYAL COLLEGE OF PHYSICIANS OF LONDON, Pall Mall East, S.W.—December 7, 5 p.m., "*The History of Some Therapeutic Procedures: Cupping and Leeching*," FitzPatrick Lecture by Dr. William Brockbank.

ROYAL EYE HOSPITAL, St. George's Circus, Southwark, London, S.E.—December 7, 5 p.m., "*Artificial Eyes*," by Mr. G. C. Pritchard.

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL, Hyde Park Corner, London, S.W.—December 7, 4.30 p.m., lecture-demonstration on psychiatry by Sir Paul Mallinson.

●SOCIETY OF APOTHECARIES OF LONDON, Black Friars Lane, Queen Victoria Street, E.C.—December 7, 3.30 p.m., "*The Medical Aspects of Peripheral Vascular Disease*," by Sir Horace Evans; 5 p.m., "*The Surgery of Peripheral Arterial Disease*," by Sir James Paterson Ross.

WINGFIELD-MORRIS ORTHOPAEDIC HOSPITAL: NUFFIELD ORTHOPAEDIC CENTRE, Oxford.—December 7, 8.30 p.m., "*The Treatment of 'Intractable' Spasticity*," by Dr. L. Guttmann.

WREXHAM AND DISTRICT CLINICAL SOCIETY.—At Wynnstay Arms Hotel, Wrexham, December 7, 7.30 p.m., "*Epidemiological Aspects of Tuberculosis*," by Dr. C. O. Stallybrass.

Friday

INSTITUTE OF OPHTHALMOLOGY, Judd Street, London, W.C.—December 8, 5.30 p.m., "*Structure and Function of the Cornea*," by Dr. H. Davson.

KING'S COLLEGE HOSPITAL MEDICAL SCHOOL, Denmark Hill, London, S.E.—December 8, "*The Spine*," Legg Memorial Lecture by Sir Thomas Fairbank.

●MAIDA VALE HOSPITAL MEDICAL SCHOOL, London, W.—December 8, 5 p.m., clinical neurological demonstration by Dr. Anthony Feiling.

ROYAL EYE HOSPITAL, St. George's Circus, Southwark, London, S.E.—December 8, 4.15 p.m., "*Pathology*," by Miss M. Savory.

●ROYAL EYE HOSPITAL, St. George's Circus, Southwark, London, S.E.—December 8, 5.30 p.m., "*Physiology of the Eye*."

ROYAL MEDICAL SOCIETY, 7, Melbourne Place, Edinburgh.—December 8, 8 p.m., Hat Night.

ROYAL SANITARY INSTITUTE.—At Newe Hall, Pilgrim Street, Newcastle-upon-Tyne, December 8, 10 a.m., papers: "*A Home of One's Own*," by Dr. J. V. Walker; "*Drains and Sewers—The Legal Aspect*," by Mr. L. Mair. Afternoon: visits.

●SOCIETY OF APOTHECARIES OF LONDON, Black Friars Lane, Queen Victoria Street, E.C.—December 8, 3.30 p.m. and 5 p.m., "*Thyroid and Parathyroid Diseases*," by Sir Henry Cohen.

Saturday

KENT PAEDIATRIC SOCIETY.—At Star Hotel, Maidstone, December 9, 2.30 p.m., "*The Value of Intelligence Testing*," by Mr. M. B. Shapiro.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Elias.—On November 13, 1950, to Dr. Mary Elias (formerly Wiggins), wife of Major T. J. G. Elias, of 29, Firs Drive, Cranford, Middlesex, a son—David Robin Cliveden.

Finlay.—On November 24, 1950, at the Royal Hospital for Women, Sydney, Australia, to Francesca Maxwell (formerly Best), wife of Donald M. L. Finlay, M.B., a daughter.

Hargrove.—On November 16, 1950, at the Hill Nursing Home, Reading, to Elizabeth (formerly Corbett-Lowe), wife of Dr. Peter Hargrove, a daughter—Carole Susan.

Mackay.—On November 16, 1950, to Viola (formerly Shafto), wife of Dr. Hugh Mackay, Gladwynne, Birtley, Co. Durham, a daughter.

MARRIAGES

Griffiths—Poulton.—On November 11, 1950, at Cheltenham, Eric Probert Griffiths M.R.C.S., L.R.C.P., D.C.H., D.R.C.O.G., to Elizabeth Ann Poulton.

Shepherd—Graham.—On November 18, 1950, at Broughty Ferry, William Shepherd M.B., Ch.B., to Shirley Anne, eldest daughter of H. A. Graham, M.D., F.R.C.S.Ed.

DEATHS

Broadley.—On November 23, 1950, at 2, Beech Hill Road, Sheffield, John Broadley, M.B., F.R.C.S.Ed.

Brophy.—On November 16, 1950, at 94, Wimbledon Hill Road, London, S.W., Cyril Mary Brophy, M.C., F.R.C.S.

Clark.—On November 15, 1950, in Glasgow, John Sawers Clark, M.C., M.B., Ch.B., D.P.H., of Carnock, Willow Avenue, Lenzie, Dunbartonshire, late of Sittingbourne, West Wickham, and Newmilns, Ayrshire.

Douglas.—On November 20, 1950, at Royal Infirmary, Edinburgh, Andrew Douglas, M.B., Ch.B.

Murray.—On November 20, 1950, in a nursing-home, Brighton, James Alexander Murray, M.D., F.R.S., aged 76.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Athletes and "Heart Strain"

Q.—*In athletic circles laymen often speak of sustaining a "strained heart" following some violent effort. Does this condition exist? If so, how does one recognize it, and what is the exact pathology?*

A.—It is not possible for a healthy young adult to strain his heart in the performance of heavy exercises. The effect of heavy exercise, such as rowing in the Boat Race, is often to cause the individual to become collapsed. In such cases, if there is any cardiac dilatation, which is questionable, this is quite transitory. The collapse is partly vasomotor and partly psychological in origin. There is also a transitory oxygen debt in the body.

If an individual is of the nervous type predisposed to effort syndrome, there is no doubt that physical overstrain may bring out the symptoms of this condition. This again causes no physical change in the heart but is an abnormality of the nervous system in which nervous stimuli to the heart cause undue tachycardia and nervous stimuli from the heart cause undue sensations arising from the heart beat.

Tropical Gastro-enteritis in Children

Q.—*We are losing a number of infants, about 6 months old, from gastro-enteritis in this area (Tel-el-Kebir). What treatment is recommended? At present we use intravenous saline and large doses of penicillin. Castor oil followed by sedation has not been tried recently. "Chloromycetin" was tried once, but it had no beneficial effect. Is "aureomycin" of any value in these cases, or is there any other effective antibiotic?*

A.—In hot climates where infection spreads through poor sanitation and defective food storage, gastro-enteritis continues to be a serious and fatal disease, and the younger the child the more serious it is. There is no specific cure for this disease. Castor oil followed by sedation does more harm than good. Chloromycetin and aureomycin may help in individual cases when the pathogenic organism is known, but their results are disappointing. The chief danger in the disease is in the chemical injury which comes from dehydration and electrolyte loss. The first step in treatment is to correct the dehydration by parenteral administrations of fluid, using saline, Hartmann's solution, or Darrow's solution, whichever may be indicated. If these are given intravenously great technical skill and constant supervision by both doctor and nurse are required; in the absence of adequate supervision it is better to give the fluid subcutaneously. When the pathogenic organism is not known sulphonamides can be given empirically (after the urine flow has been re-established)—or chloromycetin or aureomycin may be tried in the same way—but these are merely adjuvants. The correction of dehydration, and good nursing, are the first requirements.

Treatment of Dwarfism

Q.—*What is the treatment of dwarfism? After what age can any improvement cease to be expected?*

A.—The treatment of dwarfism is unsatisfactory. Retarded growth may be due (*a*) to deficiency of growth hormone, as in hypopituitarism, (*b*) to arrest of growth of bone and premature union of the epiphyses, as may be caused by chronic cachectic diseases in the past, and (*c*) to an inherent unresponsiveness of the growing ends of the bones to the normal growth stimulus, which may possibly be the cause of genetic or hereditary dwarfism. In the last two types there is no treatment which will be effective. In pituitary dwarfism the administration of growth hormone is the logical procedure, but the results obtained with the commercial preparations at present available are not impressive, probably on account of their low potency and inadequate dosage. Attempts may be made with doses of the order of 5 ml. of anterior pituitary growth hormone extract injected intramuscularly three to five times a week, but it is unlikely that any satisfactory therapeutic response will be obtained until pure growth hormone is available. When hypothyroidism is present this should be treated in the usual way. No improvement can ever be expected once the epiphyses have united.

Palatable Prescriptions of Iron

Q.—*What is the most palatable and yet effective prescription for iron for use in secondary anaemias? Are haemoglobin preparations any good?*

A.—It is difficult to state categorically which is the best and most palatable iron preparation. It is definitely established that soluble ferrous salts are the most active form of iron, but they are also the most astringent and most likely to cause nausea. Flavoured preparations of ferrous salts include syrup of ferrous iodide and syrup of ferrous phosphate, *B.P.C.*, 1949, and ferrous sulphate syrup, *U.S.P.*, XIV. Ferrous carbonate pills are slightly less liable to cause unpleasant side reactions than the sulphate, and absorption of iron from them is reasonably satisfactory.

Metallic iron, colloidal ferric preparations, and the scale preparations in which the iron is in a complex form and not readily ionized, all require to be given in large doses to produce effects. Solution of dialysed iron, *B.P.C.*, is a colloidal solution of ferric hydroxide and contains the equivalent of 3 to 4% of iron. This is non-irritant and non-astringent and is sometimes prescribed with two parts of glycerin.

For those patients who cannot tolerate any form of oral iron preparation or who do not appear to absorb iron from the digestive tract, the intravenous preparations "ferrivenin" and "iviron" are available.

Haemoglobin, after oral administration, is converted into haematin in the stomach and then passes through the bowel, very little, if any, being absorbed. An elixir of haemoglobin was included in the 1934 *B.P.C.*, but was so much inferior to the iron salts that it was deleted from the 1949 edition.

Vaginal Examination in Virgins

Q.—*What are the objections to examining a virgin without an anaesthetic?*

A.—The possibility of arousing erotic sensations under such circumstances is so remote that it can be dismissed. Indeed, such would be more likely to occur in a woman with sex experience. The reason for hesitating to make a pelvic examination in a virgin, even an inspection of the vulva, is that in most cases a young girl finds it acutely embarrassing, if not repulsive. Even if she is not hurt it is conceivable that she may suffer psychological trauma which may remain to cause aversion to coitus, vaginismus, and other marital difficulties in later life. Women in older age groups tend to tolerate pelvic examination better, and nowadays even in the younger age groups false modesty is less common. There can be no general rule, and the decision in each case must be based on clinical assessment of the likely reaction of a given patient. Whenever a tentative approach makes it clear that the patient is strongly averse to the examination, and that she is unlikely to co-operate, there should be no attempt at persuasion. If rectal examination does not then supply all the necessary information, vaginal examination under anaesthesia is indicated.

Ringworm of the Nails

Q.—*What is the best method of treating ringworm of the nails without surgical removal of the nails?*

A.—Nails infected with ringworm may be painted twice daily with tinct. iodi mitis, or they may be softened by soaking in a

solution of potassium permanganate (1 in 4,000) with subsequent scraping with the edge of a glass slide and the application of iodine, dithranol, or other fungicide. Fractional doses of *x* rays may be tried, either alone or with these measures, but no treatment is very successful, and treatment even after surgical removal fails in a considerable proportion of cases. Some fungi penetrate more deeply into the nail substance than others and are in consequence less easily cured.

Worn Incisors

Q.—*Can anything be done to improve the appearance when the upper incisors begin to wear down in middle age?*

A.—The remedy is the construction of porcelain or acrylic jacket crowns. The discoloured enamel is removed from the teeth and replaced by a shell of porcelain or acrylic resin. With this method of crowning the nerve of the tooth is left intact.

Allergic Rhinitis

Q.—*What investigations should be carried out to establish a diagnosis of allergic rhinitis? What is the treatment? Is there any known association between allergic rhinitis and glucose tolerance or gastric acidity?*

A.—The patient should be asked about the mode of onset and any seasonal incidence of the symptoms, and about his occupation and environment, with special reference to any food, dust, or other specific factor which might be a cause of the symptoms. Any substances suspected can be tested by appropriate cutaneous tests to ascertain if the patient is sensitive to it. If such sensitivity is established, treatment consists in avoiding the allergen where possible, a carefully graduated course of injections to desensitize the patient, or, if multiple sensitivity is present, a combination of these.

Many allergic patients have some degree of achlorhydria, and children who suffer from asthma have low blood sugars in over 60% of cases.

"Chloromycetin" and Hoarseness

Q.—*Can chloromycetin ever produce hoarseness or aphonia?*

A.—The most serious "toxic" effect of chloromycetin is the production of mucous membrane lesions. These commonly affect the tongue, mouth, and throat and give rise to infection, oedema, and pain. "Black tongue" has been described. The lesions are probably due to yeast infection, and it has been suggested that induced riboflavin deficiency may be a factor in causing these changes. Hoarseness and aphonia might well result, but the writer has not seen it reported. Less commonly, proctitis, vaginitis, and perineal irritation may occur and may persist for a considerable time after treatment is stopped. Nausea, anorexia, and diarrhoea are common symptoms during chloromycetin administration.

NOTES AND COMMENTS

Punch-drunkenness.—Dr. ERNST JOKL (Pretoria) writes: May I refer to your note in "Any Questions?" (September 30, p. 793). The point I wish to make is that punch-drunkenness is not a single syndrome. In our first communication on the subject in 1933 the late Eric Guttmann and I[1] made a distinction between two kinds of chronic impairment encountered in boxers—viz., behaviour anomalies indicative of psychopathic traits, and neurological or psychiatric conditions resulting from head injuries. As regards the former there are on record cases of "viciousness when drunk," "murder committed from jealousy," "boisterousness," "subnormal intelligence," "malingering," "vagrancy," "simple dementia," and "euphoria and delinquency." Instances are quoted in my book,[2] and Macdonald Critchley has recently contributed further evidence.[3] Sometimes there are neurological symptoms. Sometimes there are none. The question of the relation of the abnormal behaviour and boxing is often difficult to answer.[4] Conditions assumedly caused by head injuries in the ring include parkinsonism, cerebellar signs, dysarthria, epilepsy, paroxysmal headache, and hemiplegia.[5] Post-mortem studies in boxers have shown subdural haematoma (many cases), early delayed subarachnoid haemorrhage, multiple layers of coagulated blood (pachymeningitis haemorrhagica interna), haemorrhage into the pons, petechial haemorrhages into the cerebellum, petechial haemorrhages into the mid-brain, oedema of the entire brain, oedema of the medulla oblongata, bi-polar parenchymatous contrecoup lesions, laceration of the brain, and septic meningitis. *Ex definitione*, punch-drunkenness is a state of gradual deterioration. But, disregarding for the moment the psychopathic group, the cerebral lesions underlying the condition under discussion are assumed to be similar to those responsible for acute injuries. In fact, virtually every variety of symptom described in Rowbotham's textbook on head injuries[6] has been observed in boxers. The multiplicity of anomalies encountered renders unacceptable the assumption of a single syndrome of punch-drunkenness.

REFERENCES

1 *Münch. med. Wschr.*, 1933, **80**, 560.
2 *The Medical Aspects of Boxing*, 1941. Pretoria: Van Schaik.
3 *Punch-drunk Syndromes: the Chronic Traumatic Encephalopathy of Boxers*, ext. from *Hommage à Clovis Vincent*, 1949. Paris: Maloine.
4 Jokl, E., *Manpower*, 1947, **5-6**, 1.
5 *British Medical Journal*, 1949, **1**, 23.
6 *Acute Injuries of the Head*, 1949. Edinburgh: Livingstone.

Prickly Heat.—Dr. MARY E. EGERTON (Freetown, Sierra Leone) writes: I feel it is a pity that the readers of "Any Questions?" should not be reminded of the wartime discoveries with regard to the prevention of prickly heat (October 7, p. 847). By the issue of salt tablets the armies in tropical areas succeeded in reducing the incidence of all disabilities due to heat, including heat stroke and prickly heat. My own work on this subject hardly deserves mention, being infinitesimal by comparison, but I have again and again proved the efficacy of saline drinks to prevent prickly heat in the European newborn baby. All European babies born at the Princess Christian Hospital, Freetown, are at once put on to slightly hypertonic saline drinks instead of the usual boiled water, and by this means we have prevented the distressing prickly heat to which their sensitive skins are subject. Babies born elsewhere are frequently brought to us smothered in the rash, and I have found that saline by mouth is in every case an effective remedy, reducing the inflammation in the course of a day, and preventing further increase as long as it is continued. For adults extra salt (about three teaspoonfuls daily added to drinks) is also a remarkably effective remedy for heat lassitude.

Dr. C. J. WILSON (Kenya Colony) writes: In the *Journal* of October 7, "Any Questions?" (p. 847), occurs the statement: "There is no truly specific treatment for prickly heat." Can the author of this statement deny that the application of a mercurial lotion is invariably successful in curing prickly heat, and therefore can claim to be specific treatment (see *Journal*, 1948, **1**, 76, 228, 317, 525, 573, and 811)? When prickly heat is at last generally recognized for what it is—namely, a fungus infection at once curable by a mercurial application of requisite strength (my preference is for an aqueous solution of corrosive sublimate, 1 : 500)—perhaps we shall no longer be advised to smear the body with grease and avoid soap in an attempt to alleviate a condition so easily curable.

Dr. P. A. WITH (Trinidad) writes: I have just received the *Journal* for October 7, in which the statement is made that there is no specific treatment for prickly heat ("Any Questions?" p. 847). I notice that 1 : 1,500 solution of mercury perchloride is suggested. The specific treatment is: ℞ Liquor hydrarg. perchlor. 1 : 1,000; strong HCl 1 min. to each ounce of the liquor. When very young and serving in the Mesopotamia campaign in World War I, this prescription was given to me by a planter doctor who had come out on service. I saw some very severe cases, the body being swollen and accompanied with high fever. This lotion, swabbed all over the body several times a day and allowed to dry, was almost magical in 24 hours. . . .

Correction.—Reporting a meeting of the General Medical Services Committee (*Supplement*, November 18, p. 206) we erroneously said that acute primary (including influenzal) pneumonia is not notifiable. It is in fact notifiable.

All communications with regard to editorial business should be addressed to THE EDITOR, BRITISH MEDICAL JOURNAL, B.M.A. HOUSE, TAVISTOCK SQUARE, LONDON, W.C.1. TELEPHONE: EUSTON 2111. TELEGRAMS: *Aitiology, Westcent, London.* ORIGINAL ARTICLES AND LETTERS forwarded for publication are understood to be offered to the *British Medical Journal* alone unless the contrary be stated.

Authors desiring REPRINTS should communicate with the Publishing Manager, B.M.A. House, Tavistock Square, W.C.1, on receipt of proofs. Authors overseas should indicate on MSS. if reprints are required, as proofs are not sent abroad.

ADVERTISEMENTS should be addressed to the Advertisement Manager, B.M.A. House, Tavistock Square, London, W.C.1 (hours 9 a.m. to 5 p.m.). TELEPHONE: EUSTON 2111. TELEGRAMS: *Britmedads, Westcent, London.*

MEMBERS' SUBSCRIPTIONS should be sent to the SECRETARY of the Association. TELEPHONE: EUSTON 2111. TELEGRAMS: *Medisecra, Westcent, London.*

B.M.A. SCOTTISH OFFICE: 7, Drumsheugh Gardens, Edinburgh.